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Mary Hale, Supervisor, 308-4258
CM-1 Room 1E01

Voluntary Results Feedback Form

- *I am an examiner in Workgroup:* *(Example: 1610)*
- *Relevant prior art **found**, search results used as follows:*
  - ☐ 102 rejection
  - ☐ 103 rejection
  - ☐ Cited as being of interest.
  - ☐ Helped examiner better understand the invention.
  - ☐ Helped examiner better understand the state of the art in their technology.

  Types of relevant prior art found:
  - ☐ Foreign Patent(s)
  - ☐ Non-Patent Literature
    (journal articles, conference proceedings, new product announcements etc.)
- *Relevant prior art **not found**:*
  - ☐ Results verified the lack of relevant prior art (helped determine patentability).
  - ☐ Search results were not useful in determining patentability or understanding the invention.

Other Comments:

Drop off completed forms at the **Circulation Desk CM-1,** or send to Mary Hale, **CM1-1E01 or e-mail mary.hale@uspto.gov.**

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FILE COVERS 1907 - 18 Mar 2003 VOL 138 ISS 12
FILE LAST UPDATED: 17 Mar 2003 (20030317/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d stat que
L2 337 SEA FILE=REGISTRY BOLA/BI
L5 82 SEA FILE=HCAPLUS L2 OR BOLA(W)(A11 OR A20 OR HD1 OR HD6 OR LH7)
L6 82 SEA FILE=HCAPLUS L2 OR BOLA(W)(A11 OR A20 OR HD1 OR HD6 OR HD7)
L7 16 SEA FILE=HCAPLUS L5(L)L6 AND (IMMUN? OR VACCIN?)

=> d ibib abs hitrn l7 1-16

L7 ANSWER 1 OF 16 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:456806 HCAPLUS
DOCUMENT NUMBER: 137:323870
TITLE: Functional expression of a bovine major histocompatibility complex class I gene in transgenic mice
AUTHOR(S): Russell, George C.; Oliver, Robert A.; Craigmile, Susan; Nene, Vish; Glass, Elizabeth J.
CORPORATE SOURCE: Roslin Institute (Edinburgh), Roslin, Midlothian, EH25 9PS, UK
SOURCE: Veterinary Immunology and Immunopathology (2002), 87(3-4), 417-421
CODEN: VIIMDS; ISSN: 0165-2427
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Major histocompatibility complex (MHC) class I restricted cellular **immune** responses play an important role in **immunity** to intracellular pathogens. By binding antigenic peptides and presenting them to T cells, class I mols. impose significant selection on the targets of **immune** responses. Candidate **vaccine** antigens for cellular **immune** responses should therefore be analyzed in the context of MHC class I antigen presentation. Transgenic mice expressing human MHC (HLA) genes provide a useful model for the identification of

potential cytotoxic T lymphocyte (CTL) antigens. To facilitate the anal. of candidate CTL **vaccines** in cattle, we have produced transgenic mice expressing a common bovine MHC (BoLA) class I allele. The functional **BoLA-A11** gene, carried on a 7 kb genomic DNA fragment, was used to make transgenic mice by pronuclear microinjection. Three transgenic mouse lines carrying the **BoLA-A11** gene were established. Expression of the **BoLA-A11** gene was found in RNA and the A11 product could be detected on the surface of spleen and blood cells. Functional anal. of the A11 transgene product, and its ability to act as an antigen presenting mols. in the mouse host will be discussed.

REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 2 OF 16 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:276111 HCAPLUS
DOCUMENT NUMBER: 136:308527
TITLE: Methods comprising determination and matching MHC class I antigen of nuclear transfer embryo and embryo recipient for minimizing **immunological** rejection
INVENTOR(S): Davies, Christopher J.; Schlafer, Donald H.; Hill, Jonathan R.
PATENT ASSIGNEE(S): Cornell Research Foundation, Inc., USA
SOURCE: PCT Int. Appl., 103 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002029000	A2	20020411	WO 2001-US30925	20011003
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2001096528	A5	20020415	AU 2001-96528	20011003

PRIORITY APPLN. INFO.: US 2000-237673P P 20001003
WO 2001-US30925 W 20011003

AB The present invention relates to a method of minimizing **immunol.** rejection of a nuclear transfer ("NT") fetus which includes transferring a NT embryo into an embryo recipient under conditions effective for development of a NT fetus with minimal risk of **immunol.** rejection of the fetus due to a maternal anti-fetal MHC-I **immune** response. After detg. an MHC-I antigen type for a NT embryo and an MHC-I antigen type for embryo recipients, the NT embryo is either (i) transferred into a first embryo recipient having a compatible MHC-I antigen type under conditions effective for development of a NT fetus from the NT embryo, or (ii) transferred into a second embryo recipient having an incompatible MHC-I antigen type, followed by regulating MHC-I expression of the NT embryo or suppressing an **immune** response of the embryo recipient under conditions effective for development of a

nuclear transfer fetus. The method may also comprises treatment with cytokine, growth factor or **immunosuppressive** drug to inhibit **immune** response of the embryo recipient to reduce rejection.

IT **148611-61-4**, GenBank L02832 **148611-62-5**, GenBank L02833
148611-63-6, GenBank L02834 **148611-64-7**, GenBank L02835
151246-28-5, GenBank U01187 **160073-75-6**, GenBank X82671
160073-76-7, GenBank X82672 **160073-77-8**, GenBank X82673
160073-78-9, GenBank X82674 **160073-79-0**, GenBank X82675
166847-03-6, GenBank X87645 **173754-94-4**, GenBank X80933
173754-95-5, GenBank X80934 **173754-96-6**, GenBank X80935
173757-16-9, GenBank X80936 **175115-95-4**, GenBank X92870
176632-22-7, GenBank X97646 **176632-23-8**, GenBank X97647
176632-24-9, GenBank X97648 **176632-74-9**, GenBank X97649
183101-41-9, GenBank Y09205 **183101-42-0**, GenBank Y09206
183101-43-1, GenBank Y09207 **183101-44-2**, GenBank Y09208
217577-57-6, GenBank AJ010861 **217577-58-7**, GenBank AJ010862 **217577-59-8**, GenBank AJ010863 **217577-60-1**, GenBank AJ010864 **217577-61-2**, GenBank AJ010865 **217577-62-3**, GenBank AJ010866
RL: ANT (Analyte); BSU (Biological study, unclassified); DGN (Diagnostic use); PRP (Properties); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(method comprises matching MHC class I antigen of nuclear transfer embryo and embryo recipient and treatment of **immunosuppressive** agent for minimizing **immunol**. rejection)

L7 ANSWER 3 OF 16 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:818860 HCAPLUS
DOCUMENT NUMBER: 136:80679
TITLE: Complete genome sequence of Salmonella enterica serovar typhimurium LT2
AUTHOR(S): McClelland, Michael; Sanderson, Kenneth E.; Spleth, John; Clifton, Sandra W.; Latreille, Phil; Courtley, Laura; Porwolilk, Steffen; All, Johar; Daute, Mike; Du, Felyu; Hou, Shunfang; Layman, Dan; Leonard, Shawn; Nguyen, Christine; Scott, Kelsi; Holmes, Andrea; Grewal, Neenu; Mulvaney, Elizabeth; Ryan, Ellen; Sun, Hul; Florea, Lillana; Miller, Webb; Stoneking, Tamberiyn; Nhan, Michael; Waterston, Robert; Wilson, Richard K.
CORPORATE SOURCE: Sidney Kimmel Cancer Center, San Diego, CA, 92121, USA
SOURCE: Nature (London, United Kingdom) (2001), 413(6858), 852-856
CODEN: NATUAS; ISSN: 0028-0836
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Salmonella enterica subspecies I, serovar typhimurium (S. typhimurium), is a leading cause of human gastroenteritis, and is used as a mouse model of human typhoid fever. The incidence of non-typhoid salmonellosis is increasing worldwide, causing millions of infections and many deaths in the human population each year. The 4857-kilobase (kb) chromosome and 94-kb virulence plasmid of S. typhimurium strain LT2 has now been sequenced.. The distribution of close homologs of S. typhimurium LT2 genes in 8 related enterobacteria was detd. using previously completed genomes of 3 related bacteria, sample sequencing of both S. enterica serovar paratyphi A (S. paratyphi A) and Klebsiella pneumoniae, and hybridization of 3 unsequenced genomes to a microarray of S. typhimurium LT2 genes. Lateral transfer of genes is frequent, with 11% of the S.

typhimurium LT2 genes missing from S. enterica serovar Typhi (S. typhi), and 29% missing from Escherichia coli K12. The 352 gene homologs of S. typhimurium LT2 confined to subspecies I of S. enterica - contg. most mammalian and bird pathogens - are useful for studies of epidemiol., host specificity, and pathogenesis. Most of these homologs were previously unknown, and 50 may be exported to the periplasm or outer membrane, rendering them accessible as therapeutic or **vaccine** targets. The sequences are available from the GenBank database under Accession Nos. AE006468 (chromosome) and AE006471 (pSTL).

IT **384914-01-6 384941-59-7**
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(amino acid sequence; complete genome sequence of Salmonella enterica serovar typhimurium LT2)

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 4 OF 16 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:818857 HCAPLUS
DOCUMENT NUMBER: 136:15814
TITLE: Complete genome sequence of a multiple drug resistant Salmonella enterica serovar typhi CT18
AUTHOR(S): Parkhill, J.; Dougan, G.; James, K. D.; Thomson, N. R.; Pickard, D.; Wain, J.; Churcher, C.; Mungall, K. L.; Bentley, S. D.; Holden, M. T. G.; Sebaihia, M.; Baker, S.; Basham, D.; Brooks, K.; Chillingworth, T.; Connerton, P.; Cronin, A.; Davis, P.; Davies, R. M.; Dowd, L.; White, N.; Farrar, J.; Feltwell, T.; Hamlin, N.; Haque, A.; Hien, T. T.; Holroyd, S.; Jagels, K.; Krogh, A.; Larsen, T. S.; Leather, S.; Moule, S.; O'Gaora, P.; Parry, C.; Quail, M.; Rutherford, K.; Simmonds, M.; Skelton, J.; Stevens, K.; Whitehead, S.; Barrell, B. G.
CORPORATE SOURCE: The Sanger Centre, Wellcome Trust Genome Campus, Cambridge, CBIO ISA, UK
SOURCE: Nature (London, United Kingdom) (2001), 413(6858), 848-852
CODEN: NATUAS; ISSN: 0028-0836
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Salmonella enterica serovar typhi (S. typhi) is the etiol. agent of typhoid fever, a serious invasive bacterial disease of humans with an annual global burden of .apprx.16 million cases, leading to 600,000 fatalities. Many S. enterica serovars actively invade the mucosal surface of the intestine but are normally contained in healthy individuals by the local **immune** defense mechanisms. However, S. typhi has evolved the ability to spread to the deeper tissues of humans, including liver, spleen, and bone marrow. The 4,809,037-bp genome was sequenced for a S. typhi (CT18) that is resistant to multiple drugs, revealing the presence of hundreds of insertions and deletions compared with the Escherichia coli genome, ranging in size from single genes to large islands. Notably, the genome sequence identifies >200 pseudogenes, several corresponding to genes that are known to contribute to virulence in Salmonella typhimurium. This genetic degrdn. may contribute to the human-restricted host range for S. typhi. CT18 harbors a 218,150-bp multiple-drug-resistance IncH1 plasmid (pHCM1), and a 106,516-bp cryptic plasmid (pHCM2), which shows recent common ancestry with a virulence plasmid of Yersinia pestis.

IT **372036-32-3**

RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(amino acid sequence; complete genome sequence of a multiple drug resistant Salmonella enterica serovar typhi CT18)
REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 5 OF 16 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:359829 HCAPLUS
DOCUMENT NUMBER: 134:365698
TITLE: **Immune** response-eliciting methods and compositions using a heat shock protein and a bovine herpesvirus 1 epitope for protection against bovine herpesvirus 1
INVENTOR(S): Srikumaran, Subramaniam; Navaratnam, Manjula
PATENT ASSIGNEE(S): The Board of Regents of the University of Nebraska, USA
SOURCE: PCT Int. Appl., 41 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001034184	A2	20010517	WO 2000-US30359	20001103
WO 2001034184	A3	20020307		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-163725P P 19991105
AB Methods and compns. are provided for eliciting an **immune** response against bovine herpesvirus 1 epitopes. The methods comprise combining at least one heat shock protein with at least one bovine herpesvirus 1 epitope to form a purified epitope/heat shock protein complex and administration of an **immune** system-stimulating amt. of the purified epitope/heat shock protein complex. The compns. comprise a purified epitope/heat shock protein complex comprising at least one bovine herpesvirus 1 epitope complexed with at least one heat shock protein, and a pharmaceutically acceptable carrier, diluent or excipient.

L7 ANSWER 6 OF 16 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:105813 HCAPLUS
DOCUMENT NUMBER: 134:279242
TITLE: Transcription of the unique ruminant class II major histocompatibility complex-DYA and DIB genes in dendritic cells
AUTHOR(S): Ballingall, Keith T.; MacHugh, Niall D.; Taracha, Evans L. N.; Mertens, Bea; McKeever, Declan J.
CORPORATE SOURCE: International Livestock Research Institute, Nairobi, Kenya
SOURCE: European Journal of Immunology (2001), 31(1), 82-86

CODEN: EJIMAF; ISSN: 0014-2980
PUBLISHER: Wiley-VCH Verlag GmbH
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Dendritic cells (DC) constitute the most effective **immune** cell population for priming and recalling T cell responses to foreign antigens. DC patrol the peripheral tissues collecting foreign antigen for subsequent presentation by classical class II MHC mols. to T cells in the draining lymph nodes. Since the description of the DYA and DIB class II MHC genes, which are unique to ruminants, no transcript or protein have been reported. Here the authors provide evidence that these genes are transcribed in cattle and that paired transcription is restricted in afferent lymph to a functionally distinct population of DC. Anal. of lymph node, lung and thymus suggests that tissue DC also transcribe both genes. Cytokine-induced differentiation of cultured monocytes to a DC phenotype is linked with induction of both DYA and DIB transcription. This is consistent with an assocn. of their products with the potent antigen presenting capacity of these cells in cattle.

IT **269354-01-0**, GenBank AJ251357 **269354-02-1**, GenBank AJ251358
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(nucleotide sequence; cDNA sequences and transcription of unique ruminant class II major histocompatibility complex-DYA and DIB genes in lymph and tissue dendritic cells of Zebu cattle)

REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 7 OF 16 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:16316 HCAPLUS
DOCUMENT NUMBER: 134:235853
TITLE: Identification of a Cytotoxic T-Cell Epitope on the Recombinant Nucleocapsid Proteins of Rinderpest and Peste des petits ruminants Viruses Presented as Assembled Nucleocapsids
AUTHOR(S): Mitra-Kaushik, Shibani; Nayak, Rabindranath; Shaila, M. S.
CORPORATE SOURCE: Department of Microbiology and Cell Biology, Indian Institute of Science, Bangalore, 560012, India
SOURCE: Virology (2001), 279(1), 210-220
CODEN: VIRLAX; ISSN: 0042-6822
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The nucleocapsid protein (N) of morbilliviruses is not only a major structural protein but also the most abundant protein made in infected cells. The authors overexpressed the N proteins of Rinderpest virus and Peste des petits ruminants virus in E. coli, which assemble into nucleocapsids in the absence of viral RNA that resemble nucleocapsids made in the virus-infected cells. Employing these assembled structures resembling subviral particles, the authors studied the induction of both the antibody response and the cytotoxic T-lymphocyte (CTL) response in a murine model (BALB/c). A single dose of the purified recombinant nucleocapsids of both viruses in the absence of an adjuvant induces a strong CTL response. The CTLs generated are antigen specific and cross-reactive with respect to each virus and, furthermore, this CTL response is MHC class I restricted. Based on the prediction for H-2d-restricted T-cell motifs the authors tested the lysis of transfected P815 (H-2d) cells expressing a nine amino acid potential CTL epitope, by

splenic T cells in vitro restimulated with bacterially expressed RPV or PPRV N proteins. The authors extended the authors' study to the bovine system both to analyze the **immunogenicity** of these recombinant proteins in the natural hosts and to show that PBMC from cattle **vaccinated** with Rinderpest **vaccine** proliferate in vitro, in response to restimulation with sol. nucleocapsid proteins. Furthermore, the murine CTL epitope functions in the bovine system as a cytotoxic T-cell epitope. This sequence, which is conserved in the N proteins of morbilliviruses, conforms well to the predicted algorithm for some of the most common BoLA CTL antigenic peptides. (c) 2001 Academic Press.

REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 8 OF 16 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:181732 HCAPLUS
DOCUMENT NUMBER: 132:203916
TITLE: Complete genome sequence of Neisseria meningitidis serogroup B strain MC58
AUTHOR(S): Tettelin, Herve; Saunders, Nigel J.; Heidelberg, John; Jeffries, Alex C.; Nelson, Karen E.; Eisen, Jonathan A.; Ketchum, Karen A.; Hood, Derek W.; Peden, John F.; Dodson, Robert J.; Nelson, William C.; Gwinn, Michelle L.; DeBoy, Robert; Peterson, Jeremy D.; Hickey, Erin K.; Haft, Daniel H.; Salzberg, Steven L.; White, Owen; Fleischmann, Robert D.; Dougherty, Brian A.; Mason, Tanya; Ciecko, Anne; Parksey, Debbie S.; Blair, Eric; Cittone, Henry; Clark, Emily B.; Cotton, Matthew D.; Utterback, Terry R.; Khouri, Hoda; Qin, Haiying; Vamathevan, Jessica; Gill, John; Scarlato, Vincenzo; Masignani, Vega; Pizza, Mariagrazia; Grandi, Guido; Sun, Li; Smith, Hamilton O.; Fraser, Claire M.; Moxon, E. Richard; Rappuoli, Rino; Venter, J. Craig
CORPORATE SOURCE: The Institute for Genomic Research (TIGR), Rockville, MD, 20850, USA
SOURCE: Science (Washington, D. C.) (2000), 287(5459), 1809-1815
CODEN: SCIEAS; ISSN: 0036-8075
PUBLISHER: American Association for the Advancement of Science
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The 2,272,351-bp genome of Neisseria meningitidis strain MC58 (serogroup B), a causative agent of meningitis and septicemia, contains 2158 predicted coding regions, 1158 (53.7%) of which were assigned a biol. role. Three major islands of horizontal DNA transfer were identified; two of these contain genes encoding proteins involved in pathogenicity, and the third island contains coding sequences only for hypothetical proteins. Insights into the commensal and virulence behavior of N. meningitidis can be gleaned from the genome, in which sequences for structural proteins of the pilus are clustered and several coding regions unique to serogroup B capsular polysaccharide synthesis can be identified. Finally, N. meningitidis contains more genes that undergo phase variation than any pathogen studied to date, a mechanism that controls their expression and contributes to the evasion of the host **immune** system.

IT **260025-40-9 260027-95-0**
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(amino acid sequence; complete genome sequence of Neisseria meningitidis serogroup B strain MC58)

REFERENCE COUNT: 78 THERE ARE 78 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 9 OF 16 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:754849 HCAPLUS
DOCUMENT NUMBER: 134:114460
TITLE: Variation in the number of expressed MHC genes in different cattle class I haplotypes
AUTHOR(S): Ellis, S. A.; Holmes, E. C.; Staines, K. A.; Smith, K. B.; Stear, M. J.; McKeever, D. J.; MacHugh, N. D.; Morrison, W. I.
CORPORATE SOURCE: Institute for Animal Health, Compton, Newbury, Berks, RG20 7NN, UK
SOURCE: Immunogenetics (1999), 50(5/6), 319-328
CODEN: IMNGBK; ISSN: 0093-7711
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Anal. of cattle major histocompatibility complex (MHC) (BoLA) class I gene expression using serol. and biochem. methods has demonstrated a high level of polymorphism. However, anal. of class I cDNA sequences has failed to produce conclusive evidence concerning the no. and nature of expressed genes. Such information is essential for detailed studies of cattle **immune** responses, and to increase our understanding of the mechanisms of MHC evolution. In this study a selective breeding program has been used to generate a no. of MHC homozygous cattle expressing common serol. defined class I specificities. Detailed anal. of five class I haplotypes was carried out, with transcribed class I genes identified and characterized by cDNA cloning, sequence anal., and transfection/expression studies. Surface expression of the gene products (on lymphocytes) was confirmed using monoclonal antibodies of defined BoLA specificity. Phylogenetic anal. of available transcribed cattle MHC class I sequences revealed complex evolutionary relationships including possible evidence for recombination. The study of individual haplotypes suggests that certain groupings of related sequences may correlate with loci, but overall it was not possible to define the origin of individual alleles using this approach. The most striking finding of this study is that none of the cattle class I genes is consistently expressed, and that in contrast to human, haplotypes differ from one another in both the no. and compn. of expressed classical class I genes.

IT **320635-59-4 320635-60-7 320635-61-8 320635-62-9 320635-63-0 320635-64-1 320635-65-2**
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(amino acid sequence; major histocompatibility complex BoLA class I gene sequences and expression in different cattle haplotypes)

IT **183101-41-9**, Genbank Y09205 **183101-42-0**, Genbank Y09206 **183101-43-1**, Genbank Y09207 **183101-44-2**, Genbank Y09208
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(major histocompatibility complex BoLA class I gene sequences and expression in different cattle haplotypes)

IT **217577-57-6**, GenBank AJ010861 **217577-58-7**, GenBank AJ010862 **217577-59-8**, GenBank AJ010863 **217577-60-1**, GenBank AJ010864 **217577-61-2**, GenBank AJ010865 **217577-62-3**, GenBank AJ010866 **217577-63-4**, GenBank AJ010867
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL

(Biological study)
(nucleotide sequence; major histocompatibility complex BoLA class I gene sequences and expression in different cattle haplotypes)
REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 10 OF 16 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:414573 HCAPLUS
DOCUMENT NUMBER: 131:198304
TITLE: Bovine lymphocyte antigen-A11-specific peptide motif as a means to identify cytotoxic T-lymphocyte epitopes of bovine herpesvirus 1
AUTHOR(S): Hegde, Nagendra R.; Deshpande, Muralidhar S.; Godson, Dale L.; Babiuk, Lorne A.; Srikumaran, S.
CORPORATE SOURCE: Department of Veterinary and Biomedical Sciences, University of Nebraska-Lincoln, Lincoln, NE, USA
SOURCE: Viral Immunology (1999), 12(2), 149-161
CODEN: VIIMET; ISSN: 0882-8245
PUBLISHER: Mary Ann Liebert, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Major histocompatibility complex (MHC) class I mols. present 8-10-mer viral peptides to antiviral cytotoxic T lymphocytes (CTLs). Identification of the allele-specific peptide motifs (ASPMs) of class I mols. enables the prediction of potential CTL epitopes of a virus from its protein sequences. Based on the bovine herpesvirus 1 (BHV-1) protein sequences that conform to the **BoLA-A11** ASPM that the authors identified previously, potential CTL epitopes of BHV-1 were synthesized for use in cytotoxicity assays with CTLs from BHV-1-**immunized** calves. A peptide binding assay used to select the peptides that are most likely to be CTL epitopes categorized the peptides into groups of high, intermediate, and low binding capacity. Synthetic peptides stimulated lymphocytes from BHV-1-**immunized** calves to secrete interferon-.gamma.. Groups of peptides from the major glycoproteins of BHV-1 restimulated CTLs in vitro and sensitized targets for lysis by restimulated bulk CTLs.
REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 11 OF 16 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:454370 HCAPLUS
DOCUMENT NUMBER: 127:172784
TITLE: Computer simulations to identify in polyproteins of FMDV OK1 and A12 strains putative nonapeptides with amino acid motifs for binding to BoLA class I A11 and A20 haplotype molecules
AUTHOR(S): Becker, Yechiel
CORPORATE SOURCE: Department Molecular Virology, Institute Microbiology, Faculty Medicine, Hebrew University Jerusalem, Jerusalem, Israel
SOURCE: Virus Genes (1997), 14(2), 123-129
CODEN: VIGEET; ISSN: 0920-8569
PUBLISHER: Kluwer
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The computer program "Findpatterns" was used to search food-and-mouth disease virus- (OK1 and A12 strains) coded structural and nonstructural proteins for the availability of putative proteasome-generated nonapeptides with motifs reported for BoLA class I A11 and A20 haplotypes.

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These BoLA class I A11 and A20 nonapeptide motifs are identical to motifs of nonapeptides that interact with the peptide binding grooves of HLA class I B35 and B27 haplotypes, resp. The computer findpattern program was used to analyze the FMDV-coded polyproteins for proteolytically cleavable nonapeptides with motifs for binding to the peptide binding grooves of BoLA class I A11 or 20 haplotypes. The computer simulations revealed that FMDV-infected cells (keratinocytes and antigen presenting cells, e.g., dendritic Langerhans cells in bovines) may be able to present viral nonapeptides to CD8+ cytolytic T cells (CTLs) in a BoLA-restricted manner. The role of the cellular arm of the **immune** response in the protection of bovines against FMDV is not known. Thus, the present computer anal. may encourage further expts. to develop a new generation of FMDV nonapeptide **vaccines** to stimulate the anti-FMDV cytolytic T cell response in bovine so that would complement the humoral **immune** response achieved by **immunization** with the inactivated virus **vaccine**.

L7 ANSWER 12 OF 16 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:454351 HCAPLUS
DOCUMENT NUMBER: 127:175108
TITLE: The use of bovine MHC class I allele-specific peptide motifs and proteolytic cleavage specificities for the prediction of potential cytotoxic T lymphocyte epitopes of bovine viral diarrhea virus
AUTHOR(S): Hegde, Nagendra R.; Srikumaran, Subramaniam
CORPORATE SOURCE: Department Veterinary Biomedical Sciences, University Nebraska-Lincoln, Lincoln, NE, 68583-0905, USA
SOURCE: Virus Genes (1997), 14(2), 111-121
CODEN: VIGEET; ISSN: 0920-8569
PUBLISHER: Kluwer
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Cell mediated **immunity** (CMI) is crucial for the defense against viruses. Cytotoxic T lymphocytes (CTLs) play a major role in CMI. They recognize endogenous antigenic peptides presented by antigen presenting cells in assocn. with the major histocompatibility complex (MHC) class I mols. The elucidation of the sequence of CTL epitopes of viruses should help in designing better **vaccines**. In this study, we have identified candidate epitopes restricted by five bovine MHC class I mols. that are potentially available for presentation to CTLs. The candidate peptide epitopes were identified by using the computer programs available as a part of the Genetics Computer Group package and applying the information on allele-specific peptide motifs and intracellular enzymic cleavage patterns to the bovine viral diarrhea virus polyprotein. Several candidate peptides were found for each of the bovine lymphocyte antigens (**BoLA**)-**A11**, -A20, -HD1, and -HD6 whereas no peptide was found for **BoLA-HD7**. Based on this finding, the probable contribution of genomic segments of BVDV to the CTL response and strategies for recombinant **vaccines** are discussed.

L7 ANSWER 13 OF 16 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:329957 HCAPLUS
DOCUMENT NUMBER: 127:3982
TITLE: Characterization of cattle cDNA sequences from two DQA loci
AUTHOR(S): Russell, George C.; Gallagher, Angela; Craigmile, Susan; Glass, Elizabeth J.
CORPORATE SOURCE: Roslin Inst., Midlothian, EH25 9PS, UK
SOURCE: Immunogenetics (1997), 45(6), 455-458

CODEN: IMNGBK; ISSN: 0093-7711
PUBLISHER: Springer
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Full-length DQA cDNA sequences were obtained from a pair of cattle that had well-characterized responses to **immunization** with a model peptide antigen derived from foot-and-mouth disease virus. New alleles were named DQA*0101, DQA*1201, and DQA*2201 and phylogeny of antigen BoLA-DQA, OLA-DQA (sheep), and BoLA-DRA alleles was derived.
IT **190209-96-2 190209-97-3 190209-98-4**
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(amino acid sequence; characterization of cattle cDNA sequences from two DQA loci)
IT **181011-53-0**, GenBank Y07820 **181011-54-1**, GenBank Y07819
181014-31-3, GenBank Y07898
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); OCCU (Occurrence)
(nucleotide sequence; characterization of cattle cDNA sequences from two DQA loci)

L7 ANSWER 14 OF 16 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:72877 HCAPLUS
DOCUMENT NUMBER: 126:143035
TITLE: Identification of potential CTL epitopes of bovine RSV using allele-specific peptide motifs from bovine MHC class I molecules
AUTHOR(S): Gaddum, R. M.; Ellis, S. A.; Willis, A. C.; Cook, R. S.; Staines, K. A.; Thomas, L. H.; Taylor, G.
CORPORATE SOURCE: Inst. Animal Health, Compton, Newbury, RG20 7NN, UK
SOURCE: Veterinary Immunology and Immunopathology (1996), 54(1-4), 211-219
CODEN: VIIMDS; ISSN: 0165-2427
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Respiratory syncytial virus (RSV) is a major cause of lower respiratory tract infection in young infants and housed calves. Depletion of CD8+ lymphocytes from calves inhibited their ability to clear the virus from the nasopharynx and lungs. To study these cells further, a cytotoxic T lymphocyte (CTL) assay was established. CTL could be demonstrated in the peripheral blood of gnotobiotic calves 7-10 days post infection (p.i.) with RSV and in lungs 10 days p.i. This response was both MHC-restricted and virus-specific. Following sepn. of the lung lymphocytes by magnetic activated cell sorting, it was shown that the cytolytic activity was mediated by cells of the CD8+ phenotype. To identify epitopes recognized by bovine CTL, the consensus motifs from MHC class I alleles were identified. CDNA libraries were constructed and screened for full length class I sequences. The isolated cDNA clones were then transfected into mouse P815 cells and the expressed product **immunopptd**. and matched with a serol. specificity. The bovine MHC class I mols. were isolated from lysed transfected cells by affinity chromatog., using a monoclonal antibody specific for bovine MHC class I, and bound peptides were sepd. by reverse-phase HPLC. Anal. of the protein sequences of bovine RSV for the defined motifs has identified potential CTL epitopes.

L7 ANSWER 15 OF 16 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:759606 HCAPLUS
DOCUMENT NUMBER: 126:58565

TITLE: Prediction of potential cytotoxic T lymphocyte epitopes of bovine herpesvirus 1 based on allele-specific peptide motifs and proteolytic cleavage specificities
AUTHOR(S): Hegde, Nagendra R.; Sirkumaran, Subramaniam
CORPORATE SOURCE: Dep. Veterinary and Biomed. Sci., Univ. Nebraska-Lincoln, Lincoln, NE, 68583-0905, USA
SOURCE: Virus Genes (1996), 13(2), 121-133
CODEN: VIGEET; ISSN: 0920-8569
PUBLISHER: Kluwer
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Major histocompatibility complex (MHC) class I mols. present endogenous peptides ot cytotoxic T lymphocytes (CTLs). Elucidation of CTL epitopes of intracellular pathogens helps in designing better **vaccines** to control economically important human and animal diseases. In this study, candidate epitopes that are potentially available for presentation to the CTLs via five bovine MHC class I mols. have been identified. This was accomplished by using the computer programs "Find-patterns" and "Petidestructure" of GCG package and applying the information on cleavage patterns of cytosolic and endoplasmic reticulum proteases and peptidases as well as MHC class I allele-specific peptide motifs on 23 bovine herpesvirus-1 (BHV-1) proteins available on protein sequence database. Several candidate peptides were found for each of the bovine lymphocyte antigens (**BoLA**)-**A11**, -A20, -HD1, and -HD6 whereas no peptide was found for **BoLA-HD7**. Majority of the candidate peptides were from the viral glycoproteins. The contribution of such studies towards the identification of CTL epitopes of BHV-1 and other intracellular pathogens is discussed.

L7 ANSWER 16 OF 16 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1994:104301 HCAPLUS
DOCUMENT NUMBER: 120:104301
TITLE: Polymorphism in BoLA-DRB3 exon 2 correlates with resistance to persistent lymphocytosis caused by bovine leukemia virus
AUTHOR(S): Xu, Anlong; van Eijk, Michiel J. T.; Park, Chankyu; Lewin, Harris A.
CORPORATE SOURCE: Dep. Anim. Sci., Univ. Illinois, Urbana, IL, 61801, USA
SOURCE: Journal of Immunology (1993), 151(12), 6977-85
CODEN: JOIMA3; ISSN: 0022-1767
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The relation between polymorphism of the bovine lymphocyte Ag (BoLA)-DRB3 gene and resistance and susceptibility to persistent lymphocytosis (PL) caused by bovine leukemia virus (BLV) was investigated. Exon 2 of the BoLA-DRB3 gene was cloned from animals with BoLA haplotypes previously assocd. with resistance and susceptibility to PL. Sequence anal. revealed the presence of the amino acids Glu-Arg (ER) at putative Ag binding residues 70 and 71 only in BoLA haplotypes assocd. with resistance to PL. This correlation was confirmed in a case control study using an allele-specific polymerase chain reaction for the detection of ER at residues 70-71. These results provide a mol. basis for Ir gene control of resistance and susceptibility to PL and suggest that the cellular **immune** response is important in preventing the in vivo spread of BLV infection.

IT **148450-82-2**, GenBank M94922 **148450-83-3**, GenBank M94924
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Searched by M. Smith

148450-86-6, GenBank M94927 **148450-87-7**, GenBank M94928
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(nucleotide sequence of)

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               LH7)
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               OR CORONA OR ROTA OR SYNCYTIAL)
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L10  ANSWER 1 OF 1  HCAPLUS  COPYRIGHT 2003 ACS
ACCESSION NUMBER:         2002:408550  HCAPLUS
DOCUMENT NUMBER:          137:5001
TITLE:                    Vaccine compositions comprising bovine viral epitope
                          and heat shock protein for protection against bovine
                          viral diseases
INVENTOR(S):              Srikumaran, Subramaniam
PATENT ASSIGNEE(S):       The Board of Regents of the University of Nebraska,
                          USA
SOURCE:                   PCT Int. Appl., 28 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.        KIND  DATE           APPLICATION NO.   DATE
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     WO 2002041921      A2   20020530       WO 2001-US45781   20011102
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             BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
     AU 2002039462      A5   20020603       AU 2002-39462     20011102
     US 2002119163      A1   20020829       US 2001-3907      20011102
PRIORITY APPLN. INFO.:                   US 2000-245970P   P  20001103
                                         WO 2001-US45781   W  20011102
AB   The present invention relates to methods and compns. for eliciting an
     immune response against bovine viral epitopes. The methods comprise
     combining at least one heat shock protein with at least one bovine viral
     epitope to form a purified epitope/heat shock protein complex and
     administration of an immune system stimulating amt. of the purified
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epitope/heat shock protein complex. The compns. comprise, a purified epitope/heat shock protein complex comprising at least one bovine viral epitope complexed with at least one heat shock protein, and a pharmaceutically acceptable carrier, diluent or excipient.

SYSTEM:OS - DIALOG OneSearch
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File 10:AGRICOLA 70-2003/Mar
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File 34:SciSearch(R) Cited Ref Sci 1990-2003/Mar W2
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removal, customized scheduling. See HELP ALERT.
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***File 340: The Claims U.S. Patent databases have been reloaded.**
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File 440:Current Contents Search(R) 1990-2003/Mar 18
(c) 2003 Inst for Sci Info
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File 340:CLAIMS(R)/US Patent 1950-03/Mar 11
         (c) 2003 IFI/CLAIMS(R)
File 345:Inpadoc/Fam.& Legal Stat 1968-2003/UD=200309
         (c) 2003 EPO
File 351:Derwent WPI 1963-2003/UD,UM &UP=200318
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File 357:Derwent Biotech Res. _1982-2003/Mar W3
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(c) 1998 Inst for Sci Info
File 440:Current Contents Search(R) 1990-2003/Mar 18
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S2 2 RD (unique items)
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2/AB/1 (Item 1 from file: 340)
DIALOG(R)File 340:CLAIMS(R)/US Patent
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Dialog Acc No: 10175468 IFI Acc No: 2002-0119163 IFI Acc No: 2002-0030379
Document Type: C
METHODS AND COMPOSITIONS FOR PROTECTION AGAINST BOVINE VIRAL DESEASES
Inventors: Srikumaran Subramaniam (US)
Assignee: Nebraska, University of
Assignee Code: 58949
Publication (No,Date), Applic (No,Date):
US 20020119163 20020829 US 20013907 20011102
Publication Kind: A1
Priority Applic(No,Date): US 20013907 20011102
Provisional Applic(No,Date): US 60-245970 20001103

Abstract: The present invention relates to methods and compositions for eliciting an immune response against **bovine viral epitopes** . The methods comprise combining at least one **heat shock protein** with at least one **bovine viral epitope** to form a purified epitope/ **heat shock protein** complex and administration of an immune system stimulating amount of the purified epitope/ **heat shock protein** complex. The compositions comprise, a purified epitope/ **heat shock protein** complex comprising at least one **bovine viral epitope** complexed with at least one **heat shock protein** , and a pharmaceutically acceptable carrier, diluent or excipient.

2/AB/2 (Item 1 from file: 351)
DIALOG(R)File 351:Derwent WPI
(c) 2003 Thomson Derwent. All rts. reserv.

014754521
WPI Acc No: 2002-575225/200261
XRAM Acc No: C02-162877
Eliciting immune response against a bovine virus, comprises combining bovine viral epitope **and** heat shock protein **to form purified epitope/** heat shock protein **complex and administering the complex to an animal**
Patent Assignee: UNIV NEBRASKA (UYNE-N)
Inventor: SRIKUMARAN S
Number of Countries: 097 Number of Patents: 003
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week	
WO 200241921	A2	20020530	WO 2001US45781	A	20011102	200261	B
AU 200239462	A	20020603	AU 200239462	A	20011102	200263	
US 20020119163	A1	20020829	US 2000245970	A	20001103	200264	
			US 20013907	A	20011102		

Priority Applications (No Type Date): US 2000245970 P 20001103; US 20013907 A 20011102
Patent Details:
Patent No Kind Lan Pg Main IPC Filing Notes
WO 200241921 A2 E 28 A61K-047/48
Designated States (National): AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PH PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
Designated States (Regional): AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
AU 200239462 A A61K-047/48 Based on patent WO 200241921
US 20020119163 A1 A61K-039/12 Provisional application US 2000245970

Abstract (Basic): WO 200241921 A2
Abstract (Basic):
NOVELTY - Eliciting (M) an immune response against a bovine virus, involves combining at least one **bovine viral epitope** (E) and at least one **heat shock protein** (**HSP**) to form a purified epitope/ **heat shock protein** complex (I), and administering an immune system stimulating amount of (I) to an animal.
ACTIVITY - Virucide.
MECHANISM OF ACTION - Vaccine. Experimental protocols are given, but no results are given.
USE - The method and the composition are useful for eliciting an immune response against a bovine virus in a ruminant animal, e.g. Bovidae such as Bos (claimed).
pp; 28 DwgNo 0/0

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         9100323  PROTEIN?
          136242  HEAT(W)SHOCK(W)PROTEIN?
           29274  HSP
            1158  GP96
          890271  BOVINE
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      S5       30  S4 NOT S2
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          735277  VACCIN?
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              AL OR VIRUS)
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S5         30   S4 NOT S2
S6         19   S5 AND (IMMUN? OR VACCIN?)
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 6/AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2003 The Dialog Corp. All rts. reserv.

09037289   96390199   PMID: 8797278
  gamma delta T-lymphocytes and anti- heat shock protein reactivity in
 bovine leukemia virus infected cattle.
  Ungar-Waron H; Brenner J; Paz R; Moalem U; Trainin Z
  Department of Immunology, Kimron Veterinary Institute, Beit Dagan,
Israel.
  Veterinary immunology and immunopathology (NETHERLANDS)  May 1996,  51
 (1-2)  p79-87,  ISSN 0165-2427  Journal Code: 8002006
  Document type: Journal Article
  Languages: ENGLISH
  Main Citation Owner: NLM
  Record type: Completed
  Bovine leukemia virus (BLV) induces a chronic infection in cattle that
may result in persistent lymphocytosis (PL) and, sometimes, enzootic bovine
leukosis. The cellular and humoral immune responses of the host following
infection have been extensively investigated but little is known about the
involvement of gamma delta T-cells in BLV pathogenesis. The affluence of
these cells in cattle, and particularly in the peripheral blood of young
ruminants, may suggest a particular role for them in defense mechanisms. In
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this study we have examined circulating gamma delta lymphocytes that express workshop clusters 1 (WC1) and 2 (WC2). In healthy cattle the WC1 cell count tends to decrease with age and adult cattle blood has statistically lower numbers (19.0 +/- 6.6%) than that of young animals (40.1 +/- 7.2%). However, in the blood of BLV-seropositive adult cattle and mainly in BLV+ PL+ animals the population of WC1 cells is elevated compared with uninfected animals ($P < 0.007$). Likewise, the WC2 cells count is increased ($P < 0.01$) in BLV+PL+. Furthermore, we have investigated whether BLV infection up-regulates the expression of **heat shock proteins** (**HSP**) which in turn could augment the humoral response. Anti-HSP70 activity was examined in the sera of 34 BLV-infected cattle and 40 healthy controls by ELISA. Significantly higher activities ($P < 0.001$) were observed in BLV-infected cattle.

6/AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08401848 95159646 PMID: 7856294
A subunit gIV vaccine , **produced by transfected mammalian cells in culture, induces mucosal** immunity **against bovine herpesvirus-1 in cattle.**
van Drunen Littel-van den Hurk S; Van Donkersgoed J; Kowalski J; van den Hurk J V; Harland R; Babiuk L A; Zamb T J
Veterinary Infectious Disease Organization, University of Saskatchewan, Saskatoon, Canada.
Vaccine (ENGLAND) Nov 1994, 12 (14) p1295-302, ISSN 0264-410X Journal Code: 8406899
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
A truncated version of bovine herpesvirus-1 (BHV-1) glycoprotein IV (tgIV) was produced in a novel, non-destructive expression system based upon regulation of gene expression by the bovine heat-shock protein 70A (hsp70) gene promoter in Madin Darby **bovine** kidney (MDBK) cells. In this system, up to 20 micrograms ml-1 of secreted tgIV, which is equivalent to the yield from 4 x 10(6) cells, was produced daily over a period of up to 18 days. Different doses of tgIV were injected intramuscularly into seronegative calves. **Virus** -neutralizing antibodies were induced by all doses of tgIV, both in the serum and in the nasal superficial mucosa. However, the low dose (2.3 micrograms) induced significantly ($p < 0.05$) lower antibody titres than the medium (7 micrograms) and high (21 micrograms) doses. The medium and high doses of tgIV conferred protection from BHV-1 infection, as demonstrated by a significant ($p < 0.05$) reduction in clinical signs of respiratory disease and **virus** shedding in the nasal secretions postchallenge. However, the 2.3 micrograms group, although partially protected, was not significantly ($p > 0.05$) different from the placebo group. This study demonstrated the potential of an intramuscularly administered tgIV subunit **vaccine** to induce mucosal **immunity** to BHV-1 using an economic protein production system and an acceptable **vaccine** formulation. In addition, a strong correlation was observed between neutralizing antibodies in the serum and nasal superficial mucosa, **virus** shedding and clinical disease. Thus, serum neutralizing antibody levels in tgIV- **immunized** animals may be a good prognosticator of protection from BHV-1 infection and disease.

6/AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07450382 92383807 PMID: 1325086
Induction of the 68 kDa major heat - shock protein **in different Theileria annulata- and** virus **-transformed** bovine **lymphoblastoid cell lines.**
Heine L; Rebeski D E; Leibold W; Friedhoff K T; Gunther E
Abteilung Immungenetik, Universitat, Gottingen, Germany.
Veterinary immunology and immunopathology (NETHERLANDS) Aug 1992, 33 (3) p271-7, ISSN 0165-2427 Journal Code: 8002006
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Expression of the major inducible heat-shock protein of 68 kDa (hsp68) has been analyzed in peripheral blood mononuclear cells (PBMC) from cattle and in six Theileria annulata- and two **bovine** leukemia **virus** -transformed **bovine** lymphoblastoid cell lines (BoLCL). By metabolic labeling, hsp68 could be detected in PBMC and BoLCL only after heat-shock, but not under normal culture conditions. **Immunoblot** analysis with an hsp68 reactive monoclonal antibody similarly revealed a strong hsp68 response after heat-shock in BoLCL, and no hsp68 expression under normal culture conditions. Normally kept PBMC, however, were weakly positive with the antibody. The data are discussed with respect to the constitutive expression of hsp68 seen in several other cell lines.

6/AB/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

06751798 91061754 PMID: 2247066
A DNA-activated protein kinase from HeLa cell nuclei.
Carter T; Vancurova I; Sun I; Lou W; DeLeon S
Department of Biological Sciences, St. John's University, Jamaica, New York 11439.
Molecular and cellular biology (UNITED STATES) Dec 1990, 10 (12) p6460-71, ISSN 0270-7306 Journal Code: 8109087
Contract/Grant No.: R01 CA37761; CA; NCI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
A DNA-activated protein kinase (DNA-PK) was purified from nuclei of HeLa cells. Activity was associated with a single high-molecular-mass (approximately-300,000 Da) polypeptide when analyzed by gel filtration, denaturing polyacrylamide gel electrophoresis, and Western **immunoblotting** using a monoclonal antibody that also inhibits enzyme activity. Nuclear localization was indicated by subcellular fractionation and confirmed by immunofluorescence on whole cells. Double-stranded DNA stimulated phosphorylation of the 300-kDa polypeptide in purified preparations as well as phosphorylation of the exogenous substrates alpha-casein, simian **virus** 40 large T antigen, and the human **heat shock protein** hsp90. Autophosphorylation led to inactivation of the enzyme. The phosphorylation of casein was stimulated over 30-fold by DNA and was specific for serine and threonine residues. **Bovine** serum albumin and histone H1 were poor substrates for DNA-PK, and no phosphorylation of immunoglobulin G or histones other than H1 was observed. Supercoiled or heat-denatured DNA and synthetic double-stranded RNA or RNA-DNA copolymers did not stimulate casein phosphorylation by DNA-PK. Interaction of the enzyme with DNA in the absence of exogenous substrates was demonstrated by thermal inactivation and gel mobility shifts. These characteristics identify DNA-PK as distinct from other protein kinases described in the literature and suggest that activation by DNA is an important feature of the enzyme's in vivo function.

6/AB/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

04805780 85183031 PMID: 2985645
Immune **response to bovine herpes herpesvirus type 1 infections: virus-specific antibodies in sera from infected animals.**
Collins J K; Butcher A C; Riegel C A
Journal of clinical microbiology (UNITED STATES) Apr 1985, 21 (4) p546-52, ISSN 0095-1137 Journal Code: 7505564
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The **virus** specificity of antibodies against **bovine** herpes **virus** type 1 was determined with a radioimmunoprecipitation assay and serum collected from natural and experimentally induced infections. By using sequentially collected sera, the development of antibodies to 4 to 5 **viral** glycoproteins and 11 to 12 nonglycosylated proteins was followed for the first 50 days after infection. The major and most consistent responses in experimentally and naturally infected animals were to four glycoproteins with molecular weights of 102,000, 96,000, 69,000, and 55,000, as well as to a major virion 115,000-molecular-weight nonglycosylated protein. The four glycoproteins were all coprecipitated by a neutralizing monoclonal antibody and were probably involved as target antigens in **virus** neutralization. Another antigenically unrelated glycoprotein with a molecular weight of 82,000 and a nonglycosylated protein with a molecular weight of 91,000 were also precipitated, but the **immune** response to these two proteins was transient. Reactivity to gp82 was only weakly detected in serum from naturally infected animals. Contact control animals which did not contract a **bovine** herpes **virus** type 1 infection but were exposed to infected animals with signs of severe illness had antibodies which recognized gp102, **gp96** , gp69 and gp55 as well as p115. These antibodies were present in low amounts and, in contrast to infected animals, did not increase between acute and convalescent sampling.

6/AB/6 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13979417 BIOSIS NO.: 200200608238
Identification of iron-regulated outer membrane proteins of Mannheimia haemolytica by comparative 2-D electrophoresis, Western blotting, and MALDI-TOF.
AUTHOR: Zehr E S(a); Tabatabai L B(a); Frank G H(a)
AUTHOR ADDRESS: (a)Natl. Animal Disease Ctr., USDA, ARS, Ames, IA**USA
JOURNAL: Abstracts of the General Meeting of the American Society for Microbiology 102p286 2002
MEDIUM: print
CONFERENCE/MEETING: 102nd General Meeting of the American Society for Microbiology Salt Lake City, UT, USA May 19-23, 2002
SPONSOR: American Society for Microbiology
ISSN: 1060-2011
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Background: Mannheimia haemolytica(MH) inhabits the tonsils and nasal passages of healthy cattle as a small portion of the normal bacterial flora. After transport or during **viral** -induced illnesses, MH

serotype A1 can undergo a rapid, selective growth in the nasopharynx, and proceed to cause acute pneumonia. **Vaccination** with MH possessing expressed iron-regulated outer membrane proteins (IROMPs) has inhibited colonization of the nasopharynx. In **vaccinated** cattle, antibodies to IROMPs correlated with inhibition of MH colonization. A common mechanism for pathogens to obtain iron from the host is to up-regulate iron acquisition proteins. To study the role of IROMPs in colonization of the nasopharynx, IROMPs were isolated and identified. Methods: OMPs from MH grown in iron-restricted (brain heart infusion broth containing 2,2'-dipyridyl) and in iron-replete broth were treated with DNase and RNase, then precipitated with trichloroacetic acid. OMPs were subjected to 2-D electrophoresis and compared using BioRad's PD-Quest software. OMPs that were up-regulated in the iron-restricted medium (presumably IROMPs) were determined to be nonimmunoreactive or immunoreactive by Western blotting using convalescent **bovine** antiserum as a probe. Selected IROMPs were picked from gels, digested with trypsin, and analyzed by MALDI-TOF for identification using Prospector's MS-FIT software. Results: Thus far, two of the selected immunoreactive IROMPs have been identified as transferrin binding proteins, TbpA and TbpB. Additional up-regulated proteins are homologous to the TonB receptor, **heat shock proteins** , and transcription regulators of several bacterial species. Conclusion: We have combined 2-D electrophoresis, Western blotting, and mass spectroscopy to identify some nonimmunoreactive and immunoreactive IROMPs of MH. The proteins may be further utilized to study their role in MH colonization of the nasopharynx.

2002

6/AB/7 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

06781993 BIOSIS NO.: 000088091430
STABLY EXPRESSED FIPV PEPLOMER PROTEIN INDUCES CELL FUSION AND ELICITS NEUTRALIZING ANTIBODIES IN MICE
AUTHOR: DE GROOT R J; VAN LEEN R W; DALDERUP M J M; VENNEMA H; HORZINEK M C ; SPAAN W J M
AUTHOR ADDRESS: INST. VIROL. DEP. INFECT. DIS. IMMUNOL., STATE UNIV. UTRECHT, YALELAAN 1, 3584 CL UTRECHT, NETH.
JOURNAL: VIROLOGY 171 (2). 1989. 493-502. 1989
FULL JOURNAL NAME: Virology
CODEN: VIRLA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: We have established bovine papilloma virus (BPV)-transformed mouse C127 cell lines that synthesize the peplomer protein of the feline infectius peritonitis virus (FIPV) strain 79-1146. For this purpose, a new cassette expression vector pHSL, which carriers the Drosophila HSp70 promotor and the polyadenylation signal of the Moloney murine leukemia virus long terminal repeat, was constructed. Cocultivation of the BPV-transformed cell lines with FIPV-permissive feline fcwf-D cells resulted in polykaryocyte formation. Since it dependend on the presence of fcwf-D cells, binding of E2 to the cell receptor may be required for membrane fusion. E2 was synthesized as a core-glycosylated protein of 180K which was only slowly transported from the endoplasmic reticulum to the medal Golgi: of the E2-molecules labeled during a 1-hr pulse about half was still completely sensitive to endoglycosidase H after a 2-hr chase, while the remaining E2 had been chased into multiple, partially endoglycosidase H-resistant forms. Immunofluorescence studies also

indicated that most E2 was retained intracellularly. Mice **immunized** with whole lysates of the transformed cells produced FIPV-neutralizing antibodies as shown by plaque reduction.

1989

6/AB/8 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

03552561 Genuine Article#: PL791 Number of References: 39
Title: A SUBUNIT GIV VACCINE , **PRODUCED BY TRANSFECTED MAMMALIAN-CELLS IN CULTURE, INDUCES MUCOSAL** IMMUNITY **AGAINST BOVINE HERPESVIRUS-1 IN CATTLE** (Abstract Available)
Author(s): LITTLEVANDENHURK V; VANDONKERSGOED J; KOWALSKI J; VANDENHURK JV; HARLAND R; BABIUK LA; ZAMB TJ
Corporate Source: UNIV SASKATCHEWAN,VET INFECT DIS ORG/SASKATOON S7N 0W0/SK/CANADA/
Journal: VACCINE, 1994, V12, N14 (NOV), P1295-1302
ISSN: 0264-410X
Language: ENGLISH Document Type: ARTICLE
Abstract: A truncated version of **bovine** herpes **virus** -1 (BHV-1) glycoprotein IV (tgIV) was produced in a novel, non-destructive expression system based upon regulation of gene expression by the **bovine heat - shock protein** 70A (hsp70) gene promoter in Madin Darby bovine kidney (MDBK) cells. In this system, up to 20 mu g ml(-1) of secreted tgIV, which is equivalent to the yield from 4 x 10(6) cells, was produced daily over a period of up to 18 days. Different doses of tsIV were injected intramuscularly into seronegative calves. **Virus** -neutralizing antibodies were induced by all doses of tsIV, both in the serum and in the nasal superficial mucosa. However, the low dose (2.3 mu g) induced significantly ($p < 0.05$) lower antibody titres than the medium (7 mu g) and high (21 mu g) doses. The medium and high doses of tgIV conferred protection from BHV-1 infection, as demonstrated by a significant ($p < 0.05$) reduction in clinical signs of respiratory disease and **virus** shedding in the nasal secretions postchallenge. However, the 2.3 mu g group, although partially protected, was not significantly ($p > 0.05$) different from the placebo group. This study demonstrated the potential of an intramuscularly administered tgIV subunit **vaccine** to induce mucosal **immunity** to BHV-1 using an economic protein production system and an acceptable **vaccine** formulation. In addition, a strong correlation was observed between neutralizing antibodies in the serum and nasal superficial mucosa, **virus** shedding and clinical disease. prognosticator of protection from BHV-1 infection and disease.

6/AB/9 (Item 2 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

01866615 Genuine Article#: JH042 Number of References: 13
Title: INDUCTION OF THE 68 KDA MAJOR HEAT - SHOCK PROTEIN **IN DIFFERENT THEILERIA-ANNULATA-TRANSFORMED AND** VIRUS **-TRANSFORMED** BOVINE **LYMPHOBLASTOID CELL-LINES** (Abstract Available)
Author(s): HEINE L; REBESKI DE; LEIBOLD W; FRIEDHOFF KT; GUNTHER E
Corporate Source: UNIV GOTTINGEN,IMMUNGENET ABT,GOSSLERSTR 12D/W-3400 GOTTINGEN//GERMANY/; UNIV GOTTINGEN,IMMUNGENET ABT,GOSSLERSTR 12D/W-3400 GOTTINGEN//GERMANY/; TIERARZTL HSCH HANNOVER/W-3000 HANNOVER//GERMANY/; TIERARZTL HSCH HANNOVER,INST PARASITOL/W-3000 HANNOVER 71//GERMANY/

Journal: VETERINARY IMMUNOLOGY AND IMMUNOPATHOLOGY, 1992, V33, N3 (AUG), P 271-277
Language: ENGLISH Document Type: ARTICLE
Abstract: Expression of the major inducible **heat - shock protein** of 68 kDa (hsp68) has been analyzed in peripheral blood mononuclear cells (PBMC) from cattle and in six Theileria annulata- and two **bovine** leukemia **virus** -transformed **bovine** lymphoblastoid cell lines (BoLCL). By metabolic labeling, hsp68 could be detected in PBMC and BoLCL only after heat-shock, but not under normal culture conditions. **Immunoblot** analysis with an hsp68 reactive monoclonal antibody similarly revealed a strong hsp68 response after heat-shock in BoLCL, and no hsp68 expression under normal culture conditions. Normally kept PBMC, however, were weakly positive with the antibody. The data are discussed with respect to the constitutive expression of hsp68 seen in several other cell lines.

6/AB/10 (Item 1 from file: 35)
DIALOG(R)File 35:Dissertation Abs Online

01292561 AAD9314950
GENE EXPRESSION IN BOVINE LEUKEMIA VIRUS-INFECTED B LYMPHOCYTES
Author: TEUTSCH, MARK RICHARD
Degree: PH.D.
Year: 1993
Corporate Source/Institution: UNIVERSITY OF ILLINOIS AT URBANA-CHAMPAIGN (0090)
Source: VOLUME 54/01-B OF DISSERTATION ABSTRACTS INTERNATIONAL. PAGE 11. 131 PAGES

Bovine leukemia **virus** (BLV) is a type C, chronic transforming retrovirus that infects B-lymphocytes and is associated with a long latency period. We studied the transcriptional activation of BLV in primary cells and also examined whether a measurable increase in BLV expression would effect the transcription of host genes. De novo protein synthesis was inhibited by cycloheximide (CHX) for 6 h after initiating peripheral blood leukocyte (PBL) cultures to eliminate Tax-mediated transcription. Under these conditions, transcription of the doubly spliced tax/rex message was predominant and was induced by the addition of phorbol 12-myristate 13-acetate (PMA), 8-bromo-cyclic AMP (Br-cAMP) and fetal **bovine** serum. Serum-induced BLV expression was inhibited in PBL in a dose dependent fashion by the protein kinase A (PKA) inhibitor H-89. Host gene expression was classified as labile protein-dependent when transcription was modulated by CHX and protein kinase-mediated when transcription was modulated by PMA, Br-cAMP or serum. Regulation of **immunoglobulin** -μ (Ig-μ) was protein kinase-mediated, whereas major histocompatibility complex (MHC) class I and class II genes, **heat shock protein** 70 and the PKA regulatory subunits were all protein kinase-mediated as well as labile protein-dependent. Compared with animals that were seronegative to BLV antigens and seropositive without persistent lymphocytosis (PL), freshly isolated mIgM$\sp+$ cells obtained from cows with PL expressed an increase in Ig-μ mRNA and a decrease in the mRNA for Ig-λ. By contrast, these same cells showed no correlation between BLV-infection status and mRNA expression of MHC class I, class II or PKA genes. After 12 h of cell culture, mIgM$\sp+$ cells from animals with PL expressed high levels of BLV mRNA relative to animals that were seronegative and seropositive without PL. However, there was no apparent effect on host gene expression that correlated with BLV expression since, the MHC class I, class II, Ig-μ, Ig-λ and PKA RIα mRNA levels were either unchanged or decreased relative to freshly isolated cells. In previous studies, about one-third of BLV-infected cows with PL were unreactive with the MHC class

II DR-specific monoclonal antibody H4 when using the lymphocyte microcytotoxicity test (referred to as "H4$\sp-$" phenotype). By Northern blot analysis we compared mIgM$\sp+$ cells form H4$\sp+$ and H4$\sp-$ animals for steady state levels of DRA, DRB, DQA and DQB mRNA and determined that the H4$\sp-$ phenotype was not transcriptionally regulated. We conclude that BLV expression has no apparent effect on the mRNA levels of Ig, MHC or PKA genes, but that freshly isolated mIgM$\sp+$ cells from BLV-infected PL animals express increased constitutive Ig-μ mRNA levels. We propose that in vivo, activation of endogenous protein kinase pathways are sufficient to induce a break from retroviral latency by activating BLV transcription and the early stage of the life cycle.

6/AB/11 (Item 1 from file: 50)
DIALOG(R)File 50:CAB Abstracts

03270589 CAB Accession Number: 962212166
A subunit gIV vaccine **, produced by transfected mammalian cells in culture, induces mucosal** immunity **against bovine herpesvirus-1 in cattle.**
Drunen Littel-van den Hurk, S. van; Donkersgoed, J. van; Kowalski, J.; Hurk, J. V. van den; Harland, R.; Babiuk, L. A.; Zamb, T. J.
Veterinary Infectious Disease Organization, University of Saskatchewan, Saskatoon, Saskatchewan S7N 0W0, Canada.
Vaccine vol. 12 (14): p.1295-1302
Publication Year: 1994
ISSN: 0264-410X --
Language: English
Document Type: Journal article
A truncated version of **bovine** herpesvirus-1 (BHV-1) glycoprotein IV (tgIV) was produced in a non-destructive expression system based upon regulation of gene expression by the **bovine heat - shock protein** 70A (hsp70) gene promoter in Madin Darby **bovine** kidney (MDBK) cells. Up to 20 micro g/ml of secreted tgIV, which is equivalent to the yield from 4 x 106 cells, was produced daily for up to 18 days. Different doses of tgIV were injected i.m. into seronegative calves. **Virus** -neutralizing antibodies were induced by all doses of tgIV, both in the serum and in the nasal superficial mucosa. The low dose (2.3 micro g) induced significantly ($p < 0.05$) lower antibody titres than the medium (7 micro g) and high (21 micro g) doses. The medium and high doses of tgIV conferred protection from BHV-1 infection, as shown by a significant ($p < 0.05$) reduction in clinical signs of respiratory disease and **virus** shedding in the nasal secretions after challenge. The 2.3 micro g group, although partially protected, was not significantly ($p > 0.05$) different from the unvaccinated group. These results show the potential of an i.m. administered tgIV subunit **vaccine** to induce mucosal **immunity** to BHV-1 using an economic protein production system and an acceptable **vaccine** formulation. There was a strong correlation between neutralizing antibodies in the serum and nasal superficial mucosa, **virus** shedding and clinical disease. Serum neutralizing antibody levels in tgIV- **immunized** animals may be a good indication of protection from BHV-1 infection and disease. 39 ref.

6/AB/12 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE

02912548 EMBASE No: 1985106507
Immune **response to bovine herpes herpes virus type 1 infections: Virus-specific antibodies in sera from infected animals**

Collins J.K.; Butcher A.C.; Riegel C.A.
Diagnostic Laboratory, College of Veterinary Medicine and Biomedical Sciences, Colorado State University, Fort Collins, CO 80523 United States
Journal of Clinical Microbiology (J. CLIN. MICROBIOL.) (United States)
1985, 21/4 (546-552)
CODEN: JCMID
DOCUMENT TYPE: Journal
LANGUAGE: ENGLISH

The **virus** specificity of antibodies against **bovine** herpes **virus** type 1 was determined with a radioimmunoprecipitation assay and serum collected from natural and experimentally induced infections. By using sequentially collected sera, the development of antibodies to 4 to 5 **viral** glycoproteins and 11 to 12 nonglycosylated proteins was followed for the first 50 days after infection. The major and most consistent responses in experimentally and naturally infected animals were to four glycoproteins with molecular weights of 102,000, 96,000, 69,000, and 55,000, as well as to a major virion 115,000-molecular-weight nonglycosylated protein. The four glycoproteins were all coprecipitated by a neutralizing monoclonal antibody and were probably involved as target antigens in **virus** neutralization. Another antigenically unrelated glycoprotein with a molecular weight of 82,000 and a nonglycosylated protein with a molecular weight of 91,000 were also precipitated, but the **immune** response to these two proteins was transient. Reactivity to gp82 was only weakly detected in serum from naturally infected animals. Contact control animals which did not contract a **bovine** herpes **virus** type 1 infection but were exposed to infected animals with signs of severe illness and antibodies which recognized gp102, **gp96** , gp69 and gp55 as well as p115. These antibodies were present in low amounts and, in contrast to infected animals, did not increase between acute and convalescent sampling.

6/AB/13 (Item 1 from file: 340)
DIALOG(R)File 340:CLAIMS(R)/US Patent

Dialog Acc No: 2825264 IFI Acc No: 9707912
Document Type: C
METHOD FOR THE INDUCIBLE PRODUCTION OF PROTEINS IN GENETICALLY MODIFIED EUKARYOTIC HOST-CELLS MULTIPLIED IN VIVO
Inventors: Bromley Peter (CH); Dreano Michel (CH); Fischbach Michel (FR); Fouillet Xavier (FR); Padieu Prudent (FR); Voellmy Richard (US)
Assignee: Rothwell Properties Ltd GB
Assignee Code: 41451
Publication (No,Date), Applic (No,Date):
US 5614381 19970325 US 95421277 19950413
Publication Kind: A
Calculated Expiration: 20140325
Continuation Pub(No),Applic(No,Date): ABANDONED US 88228925 19880815; ABANDONED US 92830456 19920205; ABANDONED US 92972713 19921106; ABANDONED US 94197450 19940216
Priority Applic(No,Date): EP 86810455 19861015

Abstract: In the production of proteins of biological interest by means of a stress inducible gene expression unit/eukaryotic host cell system, the transformed cell lines are multiplicated by tumour growing in **immunodefficient** warm-blooded animals, after which the multiplicated cells are cultured in vitro and subjected to stress, whereby expression occurs in high yield. In vivo multiplication rates of 105-106 the innoculated quantity/2 weeks are reported without any loss of the latent inducible

expression capacity.

6/AB/14 (Item 1 from file: 351)
DIALOG(R)File 351:Derwent WPI

014107547
WPI Acc No: 2001-591759/200167
XRAM Acc No: C01-175562
Mucosally administered vaccines **containing zwitterionic detergents to induce or improve** immune **response towards antigen or hapten, especially used in antibacterial, antiviral, antiparasitic or antitumor** vaccines
Patent Assignee: FABRE MEDICAMENT SA PIERRE (FABR)
Inventor: BECK A; CORVAIA N; GOESTCH L; HAEUW J F; HAEUW J
Number of Countries: 027 Number of Patents: 003
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week	
FR 2805163	A1	20010824	FR 20002104	A	20000221	200167	B
WO 200162240	A2	20010830	WO 2001FR500	A	20010221	200167	
AU 200135729	A	20010903	AU 200135729	A	20010221	200202	

Priority Applications (No Type Date): FR 20002104 A 20000221
Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
FR 2805163	A1		26	A61K-031/14	
WO 200162240	A2	F		A61K-031/14	

Designated States (National): AU BR CA CN JP MX US ZA
Designated States (Regional): AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR

AU 200135729	A		A61K-031/14	Based on patent WO 200162240

Abstract (Basic): FR 2805163 A1
Abstract (Basic):

NOVELTY - The use of zwitterionic detergents (I) is claimed in the preparation of mucosally administered pharmaceutical composition (A) for inducing or improving the **immune** response of a mammal towards an antigen or hapten.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) a composition (specifically a **vaccine**) (A) in solid form (specifically as a suppository or ovule); and

(2) a mucosal administration device (specifically an aerosol, optionally containing a propellant) containing (A).

ACTIVITY - Virucide; Antibacterial; Antiparasitic; **Immunostimulant** .

MECHANISM OF ACTION - **Vaccine** .

USE - (A) is specifically a **vaccine** for the treatment or prophylaxis of tumors or viral, bacterial or parasitic infections (all claimed).

ADVANTAGE - (I) are non-toxic adjuvants which generate or amplify an **immune** response on mucosal administration. In presence of (I) **vaccines** are effective on mucosal (especially nasal) administration, which has the general advantages of (i) inducing specific IgA production directly at the site of infection, (ii) stimulating a systemic IgG-type response (creating a secondary barrier against infection) and (iii) being simpler to carry out than administration by injection.

pp; 26 DwgNo 0/2

6/AB/15 (Item 2 from file: 351)
DIALOG(R)File 351:Derwent WPI

013734197
WPI Acc No: 2001-218427/200122
XRAM Acc No: C01-065253
Producing an immunogenic complex for use in pestivirus subunit vaccines , having a heat shock protein coupled to a heterologous polypeptide antigen, comprises expressing the antigen in a cell subjected to heat shock stimulus
Patent Assignee: NEW SOUTH WALES MIN AGRIC & MIN LAND WAT (NEWS-N)
Inventor: COLACO C A L S; FROST M J; SHANNON A D
Number of Countries: 095 Number of Patents: 005
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week	
WO 200114411	A1	20010301	WO 2000AU988	A	20000818	200122	B
AU 200066711	A	20010319	AU 200066711	A	20000818	200136	
EP 1212349	A1	20020612	EP 2000954158	A	20000818	200239	
			WO 2000AU988	A	20000818		
ZA 200201458	A	20021030	ZA 20021458	A	20020221	200282	
JP 2003507052	W	20030225	WO 2000AU988	A	20000818	200317	
			JP 2001518740	A	20000818		

Priority Applications (No Type Date): AU 992337 A 19990819
Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
WO 200114411	A1	E	81	C07K-002/00	
AU 200066711	A			C07K-002/00	Based on patent WO 200114411
EP 1212349	A1	E		C07K-002/00	Based on patent WO 200114411
ZA 200201458	A		91	C07K-000/00	
JP 2003507052	W		88	C12N-015/09	Based on patent WO 200114411

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Abstract (Basic): WO 200114411 A1
Abstract (Basic):

NOVELTY - Producing (M1) an **immunogenic** complex (I) comprising a heat shock protein (hsp) coupled to a heterologous antigenic polypeptide involves expressing the antigenic polypeptide in a cell which has been subjected to a stimulus causing the induction of a heat shock response in the cells, and recovering the antigenic polypeptide coupled to one or more hsps from the cell or the culture medium.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a composition (II) comprising (I) obtained by (M1) and capable of inducing an **immune** response to the antigenic polypeptide in an animal or human;

(2) a composition (III) comprising a pestivirus antigen coupled to a hsp;

(3) a pharmaceutical composition (IV) comprising an **immunogenic** amount of (II) or (III); and

(4) inducing **immunocompetence** in an animal against a pathogen comprising administering (IV).

ACTIVITY - Antibacterial; antiviral; antiparasitic; antiprotozoal.

MECHANISM OF ACTION - **Vaccine** . The biological activity of (I) was tested in 22 pestivirus antibody negative, non-pregnant heifers. A group of animals were **vaccinated** twice, 4 weeks apart, with the

subunit protein **vaccine** . All animals were bled at regular intervals and the concentrations of both anti-E2 and anti-NS3 antibodies were determined using the complex-trapping-blocking enzyme linked **immunosorbant** assay (CTB-ELISA). Immediately after the second **vaccination** , the animals were synchronized for oestrus. Insemination occurred immediately after oestrus was detected. All animals were judged to have become pregnant and have developing fetuses at 11 weeks after the second **vaccination** . The heifers were then challenged with a dose of the live heterologous bovine viral diarrhea virus (BVDV) isolate. Six weeks following viral challenge, all heifers were slaughtered. The fetuses were collected from pregnant heifers. Individual fetal tissues were collected under sterile conditions. The average concentration of anti-E2 antibody plotted over time indicated that the subunit **vaccine** resulted in very high concentrations of anti-E2 antibody in the **vaccinated** group. A rapid anamnestic rise in the concentration of E2 antibody in the **vaccinated** group was observed at 7 days post challenge with the live BVD virus, which continued to rise until 9 days post challenge, where it remained at a sustainable maximum concentration. In contrast an increase in the concentration of anti-E2 antibody was only observed in the control group after challenge with the live virus. The onset of a normal response in the control group was then observed, with the average concentration of anti-E2 antibody beginning to develop at 14 days post challenge. However, a maximum response was not reached until 3 to 4 weeks post challenge. Thus the **vaccination** of pregnant heifers with the subunit **vaccine** creates an **immune** response in the heifer during the first 4 to 7 days after the viral infection. There was no anti-NS3 antibody detected in the **vaccinated** heifers after **vaccination** . All naturally infected animals develop anti-NS3 antibodies in 21 days after infection with BVDV. Since animals **vaccinated** with the subunit **vaccine** did not develop anti-NS3 antibodies, they were easily distinguishable from naturally infected animals. After challenge with the live virus, **vaccinated** heifers (7 out of 10) showed no significant development of anti-NS3 antibodies until 5 to 6 weeks post challenge. The remaining three **vaccinated** heifers developed anti-NS3 antibodies 3 to 6 weeks post challenge. However, the concentration of antibodies was significantly lower than the control group of heifers. In contrast, the control heifers (n=12) developed a normal antibody response commencing 14 to 18 days post challenge, reaching a peak 4 weeks post challenge. The results indicated that the replication of the live virus was inhibited in the subunit **vaccinated** group of heifers.

USE - A pharmaceutical composition comprising (I) is useful for inducing **immunocompetence** in an animal against a pathogen (claimed). Compositions comprising (I) are useful for inducing an **immune** response against the antigenic heterologous peptide or polypeptide and are used to **vaccinate** animals against infectious diseases such as diseases caused by bacteria or protozoa. Most preferably, a pharmaceutical composition which comprises an antigenic polypeptide of bovine viral diarrhea virus (BVDV) is useful for treating BVDV infections in cattle herds.

ADVANTAGE - The **immunogenic** complex is completely non-infectious and is safe for use in animals, including pregnant animals since baculoviruses do not infect animal cells. Therapeutics produced by the method will be cheaper to manufacture in that much higher yields of antigenic proteins can be produced from baculovirus-infected insect-cell cultures than from comparable systems and have been found to generate very strong memory responses in animals. Thus when an animal is subsequently challenged with a pathogen they mount a very rapid and strong response to that pathogen.

pp; 81 DwgNo 0/4

6/AB/16 (Item 1 from file: 357)
DIALOG(R)File 357:Derwent Biotech Res.

0305027 DBR Accession No.: 2003-06812 PATENT
New human oral cancer cell line, AMOS-III, useful for investigating the molecular basis of tobacco induced cancer, designing novel gene therapeutic strategies or testing the efficacy of retinoids for chemoprevention of oral cancer - human cancer culture and sense and antisense sequence for use in gene therapy
AUTHOR: RALHAN R; KAUR J
PATENT ASSIGNEE: RALHAN R; KAUR J 2002
PATENT NUMBER: US 20020110912 PATENT DATE: 20020815 WPI ACCESSION NO.: 2003-074682 (200307)
PRIORITY APPLIC. NO.: US 730567 APPLIC. DATE: 20001207
NATIONAL APPLIC. NO.: US 730567 APPLIC. DATE: 20001207
LANGUAGE: English
ABSTRACT: DERWENT ABSTRACT: NOVELTY - A human oral cancer cell line, AMOS-III, established and propagated in vitro from oral squamous cell carcinoma obtained from the mouth of a chronic tobacco chewer, is new. DETAILED DESCRIPTION - A new human oral cancer cell line, AMOS-III, established and propagated in vitro from oral squamous cell carcinoma obtained from the mouth of a chronic tobacco chewer, has the following marker profile: (a) positive for tumor suppressor gene product, p53; marker of invasion and metastasis, ets-1; ternary complex factor, elk; retinoic acid receptors, RXR; RAR; anti-apoptotic protein and chaperone, **HSP** 70; epithelial specific antigen, ESA; human cytokeratin, CK 14, cell cycle regulatory protein, p21; Oncogene cyclinD 1, **heat shock protein** , HSP90; transcription factor, ets-2; proliferation marker; Ki67; and (b) negative for human papilloma **virus** , HPV E6; mesenchymal cells marker, Vimentin; Low level of expression of oncogene MDM2, the p53 suppressor protein. INDEPENDENT CLAIMS are also included for: (1) producing human oral cancer cell line; or (2) a solid tumor produced by introducing into the **immune** deficient mammal, preferably mice, having T-cell **immunosuppression** . BIOTECHNOLOGY - Preferred Cell Line: The cell line exhibits 46, XY male chromosomes having 4% polyploidy on karyotype analysis. It comprises essentially of epithelial cells. It is responsive to all-trans retinoic acid (ATRA), where 50% cell death is observed the cells after treating them with ATRA at 0.1 nM concentration. Treatment with antisense HSP70 oligos exhibited induction of apoptosis. Preferred Method: Producing human oral cancer cell line comprises: (A) subjecting oral squamous cell carcinoma from the floor of mouth to the step of biopsy in Hanks Balanced Salt Solution (HBSS) as a buffer supplemented with antibiotics (penicillin and streptomycin) and amphotericin B; (B) cutting the treated tissue of step (a) into smaller pieces; (C) washing the cut tissues with solution of antibiotics; (D) introducing the washed tissues into tissue culture flasks having a medium comprising DMEM and Media 199 supplemented with fetal **bovine** serum (FBS) and growth supplements to allow the growth of cells comprising fibroblast cells that grow earlier than the epithelial cells; (E) removing the fibroblasts cells from the culture to obtain a cell line comprising essentially of epithelial cells. Removing the fibroblasts comprises: (A) lowering the FBS concentration; (B) trypsinizing the cells differentially, where the fibroblast that is bound loosely to the substratum detaches from the substratum easily; (C) treating cells with fibroblast specific antibody and then lysis of the fibroblasts by complement mediated lysis; and (D) purifying the epithelial cells by limiting dilution till one cell stage and further propagating single cell clones. The antibiotics comprise 100 U/ml penicillin and 100 mug/ml streptomycin. The medium contains 2:1 ratio of DMEM and media 199. The growth supplements contain 0.4 mug/ml hydrocortisone, 1-20

ng/ml EGF (epidermal growth factor), 5 mug/ml insulin, 1 x solution of antibiotics and 0.25 mug/ml fungizone. USE - The human oral cancer cell line, AMOS-III, is useful for: (1) investigating the basic/molecular mechanisms and pathobiology of tobacco induced cancer, which is of prime importance in the Indian context and determining biological relevance of alterations in cell cycle regulatory genes as p53, bcl-2, p21/waf1, mdm1 and HSP70 in oral cancer cells; (2) identifying genes that are differentially expressed in oral cancer; (3) designing novel gene therapy approaches for management of oral cancer; (4) testing the efficacy of retinoids for chemoprevention of oral cancer and identifying retinoid responsive genes, which are differentially expressed and provide insight into the mechanism of action of retinoids; (5) studying mechanisms implicated in invasion and metastasis or chromosomal aberrations occurring due to tobacco exposure; (6) understanding the molecular mechanisms implicated in multidrug resistance, designing novel mutimodality therapeutic regimens for better management of the disease and identifying modulators for circumvention of drug resistance; or (7) testing the efficacy of gene therapy strategies such as antisense HSP70 oligonucleotides for induction of apoptosis in oral cancer cells. Further, the supply of the human oral cancer cell lines to National and International Culture Collections gives an access of much needed in vitro experimental model system to several other laboratories/regional centers. (all claimed.) (6 pages)

6/AB/17 (Item 2 from file: 357)

0303710 DBR Accession No.: 2003-05495 PATENT

Creating protein-binding profile of test compound, to create toxicological profile indicative of compound's toxicity in vivo, involves screening expression library to identify proteins that interact with compound - plasmid-mediated Rep78 fusion protein gene transfer and expression in HEK-293 cell and Escherichia coli for protein analysis

AUTHOR: DAHIYAT B; LI M

PATENT ASSIGNEE: XENCOR INC 2002

PATENT NUMBER: WO 200268698 PATENT DATE: 20020906 WPI ACCESSION NO.: 2003-040516 (200303)

PRIORITY APPLIC. NO.: US 270781 APPLIC. DATE: 20010222

NATIONAL APPLIC. NO.: WO 2002US8023 APPLIC. DATE: 20020222

LANGUAGE: English

ABSTRACT: DERWENT ABSTRACT: NOVELTY - Creating a protein-binding profile of test compound (T) comprising contacting (T) with library of nucleic acid (NA)/protein conjugates (I), where each (I) has a fusion protein with NA modifying enzyme (II), and candidate protein (III), and an expression vector with fusion NA comprising coding sequences for (II) and (III), and enzyme attachment sequence (EAS), is new. DETAILED DESCRIPTION - Creating (M1) a protein-binding profile of a test compound (T) comprising contacting (T) with a library of NA/protein (NAP) conjugates (I), where each of (I) comprises: (a) a fusion protein comprising: (i) NA modifying (NAM) enzyme (II); and (ii) a candidate protein (III); and (b) an expression vector comprising: (i) a fusion NA comprising a coding sequence for (II); and (ii) a coding sequence for (III), and (ii) an enzyme attachment sequence (EAS), where the EAS and (II) are covalently linked; and where at least two of (I) comprise different (III), detecting binding of (T) to a (I) in the library, and identifying (III) in bound (I) by determining the nucleotide composition of the coding sequence for (III) in the bound (I), thus creating a protein-binding profile of (T) comprising a list of (III) to which (T) binds. BIOTECHNOLOGY - Preferred Method: In (M1), (II) is

preferably a Rep protein. (I) is produced by eukaryotic host cells containing the expression vectors. The coding sequence for (III) is derived from a cDNA library. (M1) further involves the step of determining the binding affinity between (T) and bound (I). USE - (M1) is useful for creating a protein-binding profile of a test compound. (M1) is useful for determining the toxicity of a compound, which involves: (a) providing: (i) first protein-binding profile of a first compound which is known to have a toxic effect in an animal species; and (ii) a second protein-binding profile of a second compound, where the first and second profiles are obtained by (M1), and the coding sequence for (III) is derived from the animal species; and comparing the first and second profiles, and a substantial similarity between the two profiles indicates that the second compound has toxic effect in the animal species; (b) providing: (i) a first protein-binding profile of the compound which is known to have a toxic effect in a first animal species, where the first profile is obtained by (M1) in which the coding sequence for (III) is derived from first animal species; and (ii) second protein-binding profile of the compound is obtained by (M1) in which the coding sequence for (III) is derived from second animal species; comparing the first and second profiles, and a substantial similarity between the two profiles indicates that the compound has toxic effect in the second animal species; (c) providing: (i) a first protein-binding profile of the compound which is known to have a toxic effect in a first organ of an animal species, and the first profile being obtained by (M1), in which the coding sequence for (III) is derived from first organ; and (ii) second protein-binding profile of the compound, the second profile being obtained by (M1), in which the coding sequence for (III) is derived from a second organ of the animal species; comparing the first and second profiles, where substantial similarity between the two profiles indicates that the compound has toxic effect in the second organ; (d) providing: (i) a first protein-binding profile of the compound which is known to have a toxic effect in an animal species at a first developmental stage, and the first profile being obtained by (M1), in which the coding sequence for (III) is derived from the first animal species at the first developmental stage: and (ii) second protein-binding profile of the compound, the second profile being obtained by (M1), in which the coding sequence for (III) is derived from the animal species at a second developmental stage; comparing the first and second profiles, where substantial similarity between the two profiles indicates that the compound has toxic effect in the second animal species at the second developmental stage; (e) providing a first protein-binding profile of the compound, the profile being obtained by (M1); and (f) determining whether the protein-binding profile includes one or more of the following: liver enzymes, cytochrome proteins, proteins encoded by multiple drug resistance genes, p450, and proteins associated with glutathione regulation, DNA repair, transcription regulation, structural maintenance, cell cycle control, and/or apoptosis, **heat shock proteins**, and housekeeping genes, where such inclusion is indicative of the compound's with a toxic effect (all claimed). (M1) is therefore useful for carrying out species-specific toxicology tests, differential organ interaction tests, developmental stage-specific toxicity tests, and individualized toxicity tests. The method allows for the creation of a protein-binding profile of the test compound e.g., any synthetic or natural compound including an organic or inorganic compound, a peptide or nucleic acid, a metabolite, a drug derivative, or a chemical entity. The compound can be drug, drug candidate, or an ingredient in human consumable (e.g., food, textile, cosmetics, flavors, fragrances, emulsifiers, surfactants, and detergents); compounds that in come in contact in with humans and other animals (e.g., pets and farm stock) such as pesticides, fertilizers, feed additives, antibiotics, herbicides, fungicides, polymer additives,

and environmental proteins. These profiles can then be used to evaluate and predict toxicity and other biological activities of the test compounds. The toxicity profiling information can be used to predict toxicity of a compound in a different species, e.g., to extrapolate the toxicity effects of a compound from one species to another.The information can also be used to predict the toxicity of a compound in individuals of the same species that are under different physiological conditions (e.g., age, sex, and/or disease states, e.g., to identify individuals particularly susceptible to the toxicity. Preferably, the method is used to assess the safety of a candidate drug prior to clinical trial, and to improve clinical trials by allowing determination of toxic or unanticipated responses in humans early in a clinical trial to avert tissue toxicity. The methods also helps evaluate and predict toxicity of chemicals in environmental or occupational settings such as in manufacturing and agriculture. ADVANTAGE - By knowing the proteins that (T) can bind to, a toxicological profile of this compound can be created that is indicative of the toxicity of the toxicity of the compound in vivo. Such profiling information will improve the risk assessment process in drug development as well as in setting environmental and occupational health standards. The method provides information on the direct cellular targets of (T). EXAMPLE - Plasmid pML2000, encoding a recombinant Rep78-coding DNA fusion fragment, was constructed. Expression of pML2000 in host cells allows for expression of the modified Rep78 protein as a fusion protein with a referenced partner, and covalent attachment of the fusion protein to the attachment signal in a **viral** or plasmid vector. The ability to form DNA-eREP complexes was tested. Host cells were transfected with two plasmids, pML2000 and pML2000(DELTAITR), individually and in combination. For each of the referenced transfections, a total of 10 microg DNA was added in order to achieve a similar level of eREP protein expression. At 48 hours after transfection, the cells were harvested and protein lysates were prepared. To test covalent binding between the expressed eREP and the plasmid DNA, the lysates were first boiled for 5 minutes and immediately chilled on ice. An aliquot of boiled lysate from each sample was mixed the anti-REP antibody followed by incubation with an excess amount of protein A agarose. After an extensive wash, the protein A agarose beads were transferred to polymerase chain reaction (PCR) tubes. The presence of bound plasmid was tested by PCR to amplify the regions specific for either plasmid. The transfected plasmid pML2000 was precipitated by protein A agarose while the pML2000 (DELTAITR) was not precipitated. The formed eREP-pML2000 complex was heat-resistant, consistent with the covalent bonding between eREP and the expression plasmid pML2000. To retrieve a protein with a desired property, a chemical moiety, for example, FK506 was purchased and chemically attached to biotin. After conjugation, the compound was purified by standard chromatographic techniques. To immobilize the compound, immobilon-4-96-well plates first were coated with 10 mug/ml streptavidin (SA). Following the coating, the biotinylated-FK506 in phosphate buffered saline (PBS) was added to saturate all binding sites. After removal of the excess biotinylated-FK506, the coated wells then were blocked with 1% **bovine** serum albumin (BSA) in PBS. After washing, the immobilized compound was ready for affinity selection. A library of lysates comprising fusion enzyme-expression vector complexes were prepared by first transfecting approximately 108 mammalian HEK cells with cDNA libraries prepared from mouse RNA. At 48 hours post-transfection, the cells were harvested and collected by centrifugation. The cells were lysed in the presence of proteinase inhibitors. Total crude lysate was clarified. The prepared cell lysates were used with immobilon-4 wells coated with biotinylated-FK506. After incubation with the biotinylated-FK506, the lysate was removed from the immobilon-4 plates. The wells were then washed extensively with PBS.

The bound fusion enzyme-expression vector complexes were released from the biotinylated-FK506 by incubation with 1% trypsin. The recovered DNA was extracted twice with Tris-buffered phenol and precipitated. The precipitated DNA was washed once with 70% ethanol and transformed into bacteria using electroporation. cDNA peptides with desired properties can be characterized by employing enzyme linked **immunosorbent** assay (ELISA) procedures using standard protocols and antibodies specific for the nucleic acid modifying (NAM) enzyme, e.g., Rep78. Thus, if a cDNA clone encodes a peptide that interacts with FK506. The cell lysate comprising the referenced plasmid DNA will be specific to FK506 coated wells, but not streptavidin (SA)-coated or other negative control coated wells. After two rounds of affinity panning, individual colonies of bacterial transformants were randomly selected. Overnight cultures from single colonies in 3 ml of LB ampicillin (100 microg/ml) were used to isolate DNA. Expression of the eREP-variant peptide fusion proteins was achieved by transient transfection into HEK 293 cells. At 48 hours post-transfection, cell lysates were prepared. Clarified lysates were used immediately for ELISA. To initiate binding of the fusion enzyme-expression vector complexes to the well surface, 100 microl of 1:10 diluted lysates was added to each well. The binding of the eREP cDNA-binding portion peptide of the fusion enzyme was detected using rabbit anti-REP antibody. The plate was developed by adding alkaline phosphatase-conjugated goat anti-rabbit antibody. Control plasmids, e.g., plasmids not comprising the coding sequence for a FK506-binding peptide, did not induce a signal in the ELISA assay. Fusion enzymes comprising a peptide with the target property, FK506 binding, were identified by the ELISA assay. (109 pages)

6/AB/18 (Item 3 from file: 357)
DIALOG(R)File 357:Derwent Biotech Res.

0299767 DBR Accession No.: 2003-01551 PATENT
Nucleic acid molecule encoding a fusion polypeptide that promotes processing via the Major Histocompatibility Complex class I pathway and/or promotes activity of an antigen presenting cell, useful as vaccine **for cancer and viral infections - vector-mediated gene transfer and expression in host cell for recombinant** vaccine **and gene therapy**
AUTHOR: WU T; HUNG C
PATENT ASSIGNEE: UNIV JOHNS HOPKINS 2002
PATENT NUMBER: WO 200261113 PATENT DATE: 20020808 WPI ACCESSION NO.: 2002-619261 (200266)
PRIORITY APPLIC. NO.: US 265334 APPLIC. DATE: 20010201
NATIONAL APPLIC. NO.: WO 2002US2598 APPLIC. DATE: 20020201
LANGUAGE: English
ABSTRACT: DERWENT ABSTRACT: NOVELTY - A new nucleic acid molecule (I) encoding a fusion polypeptide useful as a **vaccine** composition, comprising a first nucleic acid sequence encoding a first polypeptide or peptide that promotes processing via the Major Histocompatibility Complex class I pathway (MHC-I-PP) and/or promotes development or activity of an antigen presenting cell (APC), is new. DETAILED DESCRIPTION - A new nucleic acid molecule (I) encoding a fusion polypeptide useful as a **vaccine** composition, comprising a first nucleic acid sequence encoding a first polypeptide or peptide that promotes processing via the Major Histocompatibility Complex class I pathway (MHC-I-PP) and/or promotes development or activity of an antigen presenting cell (APC). The nucleic acid molecule optionally comprises fused in frame with the first nucleic acid sequence, a linker nucleic acid sequence encoding a linker peptide, and a second nucleic acid sequence that is linked in frame to the first nucleic acid

sequence or to the linker nucleic acid sequence and that encodes an antigenic polypeptide or peptide. INDEPENDENT CLAIMS are also included for the following: (1) an isolated nucleic acid molecule that under stringent conditions hybridizes simultaneously with at least part of the nucleic acid sequence and at least part of the second, first and/or linker nucleic acid sequence, or at least part of the second nucleic acid sequence and part of the linker nucleic acid sequence; (2) an expression vector comprising (I) operatively linked to a promoter, and optionally, additional regulatory sequences that regulate expression of the nucleic acid in eukaryotic cell; (3) a cell which has been modified to comprise (I) or the expression vector of (2); (4) a particle comprising (I) or the expression vector of (2); (5) a fusion or chimeric particle comprising a first polypeptide that promotes processing via the MHC class I pathway and/or promotes development or activity of an APC, and a second polypeptide comprising an antigenic peptide or polypeptide; (6) a pharmaceutical composition capable of inducing or enhancing an antigen-specific **immune** response comprising a pharmacologically or **immunologically** acceptable excipient in combination with: (a) the expression vector of (2) and (I); (b) the cell of (3); (c) the particle of (4); (d) the fusion or chimeric polypeptide of (5); or (e) any combination of (a)-(d); (7) a method of inducing or enhancing an antigen specific **immune** response in cells or in a subject comprising contacting the cells with, or administering to the subject the pharmaceutical composition of (6), therefore inducing or enhancing the response; (8) a method of increasing the numbers or lytic activity of CD8+ CTLs specific for a selected antigen comprising administering the pharmaceutical composition of (6), where the nucleic acid molecule, the expression vector, the cell, the particle or the fusion or chimeric polypeptide comprises the selected antigen, and the selected antigen comprises an epitope that binds to, and is presented on the cell surface by, MHC class I proteins; and (9) a method of inhibiting growth or preventing re-growth of a tumor in a subject comprising administering the pharmaceutical composition of (6), where the nucleic acid molecule, the expression vector, the cell, the particle or the fusion or chimeric polypeptide comprises one or more tumor-associated or tumor-specific groups present on the tumor, therefore inhibiting the growth or preventing the re-growth. WIDER DISCLOSURE - Also disclosed as new are methods for producing the fusion polypeptides, fragments and derivatives. BIOTECHNOLOGY - Preferred Nucleic Acid: The antigenic peptide of (I) comprises an epitope that binds to a MHC class I protein, which is between 8-11 amino acid residues in length. The first polypeptide or peptide is Hsp70 or Flt3 ligand (FL), and their active terminal domain, or their functional derivatives. The first polypeptide has a fully defined sequence of 623 amino acids, given in the specification, or the full length sequence of Hsp70 (GENBANK Z95324 AL123456) and encoded by nucleotides 10633-12510 of the Mycobacterium tuberculosis genome. The first polypeptide consists essentially of the C-terminal domain having a sequence from residue 517 to C-terminal amino acid residue of 623 amino acids, fully defined in the specification, or the full length native sequence of Hsp70 (GENBANK Z95324 AL123456) and encoded by nucleotides 10633-12510 of the Mycobacterium tuberculosis genome. The first polypeptide is preferably FL, and consists essentially of a fully defined sequence of 189 amino acids, given in the specification. The antigen is one which is present on, or cross-reactive with an epitope of a pathogenic organism, cell or virus. The virus is a human papilloma virus. The antigen is the Eand polypeptide of HPV-16 or its antigenic fragment. The HPV-16 E7 polypeptide is non-oncogenic. The pathogenic organism is a bacterium. The pathogenic cell is a tumor cell. The antigen is a tumor-specific or tumor-associated antigen, or any antigenic epitope. The antigen further comprises the HER-2/neu protein or its peptide, mutant p53 or a melanoma-associated antigens selected from MAGE-1,

MAGE-3, MART-1/Melan-A, Tyrosinase, gp75, gp100, BAGE, GAGE-1, GAGE-2, GnT-V and p15. (I) is preferably linked to a promoter, which is expressed in an APC. The APC is a dendritic cell. Preferred Vector: The expression vector of (2) is a viral vector or a plasmid, The plasmid is pcDNA3 which is derived from a fully defined sequence of 5361 bp, given in the specification, prior to insertion of the nucleic acid sequences encoding the first or second polypeptides. The vector is a self-replicating RNA replicon, which is a Sindbis virus self-replicating RNA replicon. The replicon is SINrep5 which is derived from a fully defined sequence of 9951 bp, given in the specification, prior to the insertion of the nucleic acid sequences encoding the first or second polypeptides. The vector is also a suicidal DNA vector, which is an alphavirus DNA vector. The alphavirus is Semliki Forest virus (SFV), which is pSCA1. The suicidal DNA is derived from a fully defined sequence of 114899 bp, given in the specification. The first encoded polypeptide or peptide is Hsp70, an active C-terminal domain, or their functional derivatives. The first polypeptide has a fully defined sequence of 623 amino acids, given in the specification, or the full length sequence of Hsp70 (GENBANK Z95324 AL123456) and encoded by nucleotides 10633-12510 of the Mycobacterium tuberculosis genome. The first polypeptide consists essentially of the C-terminal domain having a sequence from residue 517 to C-terminal amino acid residue of 623 amino acids, fully defined in the specification, or the full length native sequence of Hsp70 (GENBANK Z95324 AL123456) and encoded by nucleotides 10633-12510 of the Mycobacterium tuberculosis genome. The self-replicating RNA replicon also encodes HPV protein E7, and has the nucleotide sequence of 12110 bp, fully defined in the specification. The suicidal DNA vector also encodes HPV protein E7, and has the nucleotide sequence of 13599 bp, fully defined in the specification. The first encoded polypeptide or peptide is the Flt3 ligand, the extracellular domain, or their functional derivatives. The first encoded polypeptide consists essentially of the extracellular domain of FL having a fully defined sequence of 189 amino acids, given in the specification. The vector alternatively comprises a naked DNA plasmid pcDNA3 that includes the coding sequence for HPV protein E7 and the FL extracellular domain, and has a fully defined sequence of 6161 bp, given in the specification. Preferred Cell: The cell expresses the nucleic acid molecule and the fusion polypeptide. The cell is preferably an APC, which is a dendritic cell, a keratinocyte, a macrophage, a monocyte, a microglial cell, an astrocytes, or an activated endothelial cell. Preferred Particle: The particle further comprises a material which is suitable for introduction into a cell or an animal by particle bombardment. The material is gold. Preferred Polypeptide: The antigenic peptide or polypeptide comprises an epitope that binds to and is presented on the cell surface by MHC class I proteins. The first polypeptide and the antigenic polypeptide or peptide are linked by a chemical linker. The first and second polypeptide is N-terminal to the second and first polypeptide, respectively. The first polypeptide or peptide is Hsp70 or Flt3 ligand (FL), and their active terminal domain, or their functional derivatives. The first polypeptide has a fully defined sequence of 623 amino acids, given in the specification, or the full length sequence of Hsp70 (GENBANK Z95324 AL123456) and encoded by nucleotides 10633-12510 of the Mycobacterium tuberculosis genome. The first encoded polypeptide consists essentially of the extracellular domain of FL having a fully defined sequence of 189 amino acids, given in the specification. The polypeptide is encoded by (I) or the expression vector of (2). Preferred Method: The response in the method of (7) is mediated at least in part by CD8+ cytotoxic T lymphocytes (CTL) or antibodies. The subject is a human. The contacting of cells is ex vivo with the composition. The cells comprise APCs, which are dendritic cells of human origin. The APCs are isolated from a living subject. The method

further comprises administering the cells to which were contacted with the composition ex vivo to a histocompatible subject or the subject from which the cells were obtained. The administering is by intramuscular, intradermal or subcutaneous route. The composition comprises (I), the expression vector or particle, and administering is by biolistic injection. The administering is also by intratumoral or peritumoral. The method further comprises treating the subject with radiotherapy or chemotherapy. The administering in the method of (9) is intratumoral or peritumoral. ACTIVITY - Cytostatic; Virucide. A Sindbis RNA **vaccine** linking E7 with Hsp70 significantly increased expansion and activation of E7-specific CD8+ cells and NK cells, bypassing requirement for CD4+ T cell-mediated help and resulting in potent anti-tumor **immunity** against E7-expressing tumors. Mechanistic studies confirmed that the Sindbis E7/Hsp70 RNA **vaccine** induced apoptotic death of host cells and promoted processing of this apoptotic material by dendritic cells leading to significantly increased expansion and activation of E7-specific CD8+ cells. The enhanced CD8 response resulted in a state of potent anti-tumor **immunity** against an E7-expressing tumor cell line. MECHANISM OF ACTION - Gene therapy, CD8-Agonist; **Vaccine** . USE - The methods and compositions of the present invention are useful as therapeutic **vaccine** for cancer and for major viral infections, such as hepatoma and cervical cancer, that cause morbidity and mortality. They can also be used in treating animal diseases, such as equine herpesvirus, bovine viruses, Marek's disease, retroviral and lentiviral diseases and rabies, in the veterinary medicine context. ADMINISTRATION - Dosage forms suitable for internal administration is from 1 ng/kg - 10 mg/kg, preferably 0.1 microgram/kg -1 microgram/kg body weight. Routes of administration include intradermal, intravenous, intramuscular, oral, intrathecal, inhalation, transdermal, rectal, intratumoral or peritumoral. EXAMPLE - DNA fragments were isolated by cutting pc DNA3-Hsp70, pcDNA3-E7 and pcDNA3-E7/Hsp70 respectively with Xba I and Pme I restriction enzymes followed by gel recovery from the digested products. These fragments were cloned into sites of the SINrep5 vector to generate constructs. SpeI was used to linearize DNA templates for the synthesis of RNA replicons from SINrep5-Hsp70. RNA **vaccines** were transcribed in vitro and capped using SP6 RNA polymerase and capping analog from the in vitro transcription kit. After synthesis, DNA was removed by digestion with DNase I. The expression of E7 protein from SINrep5-E7 was determined by indirect ELISA. In general, the transfection efficiency in our electroporation was consistent and measured around 30%.(127 pages)

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Use of CD36 as heat shock protein (HSP) receptor as basis for identifying HSP-CP36 mediated process modulator, HSP binding to CD36 modulator, or modulator of HSP-mediated cellular signaling by CD36-expressing cells - recombinant heat shock protein receptor expression in HEK cell culture for use in drug screening and disease therapy
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(HSP) receptor as basis for: (i) identifying compound that modulates HSP-CP36 mediated process; (ii) identifying compound that modulates binding of HSP to CD36; or (iii) identifying compound that modulates HSP-mediated cellular signaling by CD36-expressing cells, is new. DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following: (1) identifying (M1) a compound that modulates an HSP-CD36 mediated process, involves contacting: (a) a test compound with a heat shock protein and CD36; or (b) a test compound with **HSP** and CD36-expressing cell; and measuring the level of CD36 activity or expression (of the cell), such that if the level of measured activity or expression differs from the level of CD36 activity in the absence of the test compound, then a compound that modulates an **HSP** -CD36-mediated process, is identified; (2) identifying (M2) a compound that modulates the binding of a **HSP** to CD36, involves: (a) contacting **HSP** with CD36, or its fragment, or analog, derivative or mimetic, in the presence of test compound; and (b) measuring the amount of **HSP** bound to CD36, such that if the measured amount of bound **HSP** differs from the amount of bound **HSP** measured in the absence of the test compound, then a compound that modulates the binding of **HSP** to CD36 is identified; (3) identifying (M3) a compound that modulates **HSP** -mediated signal transduction by CD36-expressing cells involves: (a) adding a test compound to mixture of CD36-expressing cells and a complex consisting essentially of **HSP** non-covalently associated with an antigenic molecule, under conditions conductive to CD36-mediated signal transduction; and (b) measuring the level of stimulation by CD36-expressing cells, such that if the measured level differs from the level of stimulation in the absence of the test compound, then a compound that modulates **HSP** -mediated signal transduction by CD36-expressing cells is identified (4) detecting (M4) **HSP** -CD36 related disorder in a mammal comprising measuring the level of activity from an **HSP** -CD36 mediated process in a patient sample, such that if the measured level differs from the level found in clinically normal individuals, then a **HSP** -CD36 related disorder is detected; (5) modulating (M5) an **immune** response by administering to a mammal a purified compound that modulates the interaction of **HSP** with CD36; (6) treating (M6) an autoimmune disorder by administering to a mammal in need of such treatment a purified compound that interferes with the interaction of a **HSP** with CD36; (7) treating (M7) an autoimmune disorder by administering to mammal, a recombinant cell that expresses CD36, or by decreasing signal transducing activity by functional CD36; (8) increasing the **immunopotency** of a cancer cell or an infected cell involves transforming the cell with a nucleic acid comprising a nucleotide sequence that: (a) is operably linked to a promoter; and (b) encodes a CD36 polypeptide; and administering the cell to an individual in need of treatment, so as to obtain an elevated **immune** response; (9) a recombinant cancer cell (I) or infected cell (II) transformed with a nucleic acid comprising a nucleotide sequence that is operably linked to a promoter and encodes the CD36 polypeptide; (10) identifying a CD36 fragment capable of binding a **HSP** , or **HSP** fragment capable of binding CD36; (11) identifying a CD36 fragment capable of inducing an **HSP** -CD36-mediated process; (12) identifying **HSP** fragment capable of inducing **HSP** -CD36-mediated process; (13) identifying a molecule that binds specifically to CD36; (14) screening for molecules that specifically bind to CD36; (15) identifying a compound that modulates: (a) the binding of a CD36 ligand to CD36; (b) the interaction between CD36 and CD36 ligand; (c) interaction between CD36 and a CD36 ligand; or (d) signal transduction by CD36-expressing cells; (16) modulating an **immune** response comprising administering to a mammal a purified compound that binds to CD36; (17) treating or preventing a disease or disorder comprising administering to a mammal a purified compound that binds to CD36; and (18) treating an autoimmune disorder comprising administering to a mammal, a purified compound that binds to CD36.

BIOTECHNOLOGY - Preferred Method: In (M1), the compound identified is an antagonist which interferes with the interaction of **HSP** with CD36, in which case, (M1) further involves determining whether the level interferes with the interaction of the **HSP** and CD36. The test compound employed in the method is an antibody specific for CD36 or **HSP** , a small molecule, or a peptide (P) comprising at least 5 (preferably, at least 10) consecutive amino acids of CD36 or **HSP** . Optionally, the compound identified using (M1), is an agonist which enhances the interaction of **HSP** with CD36. The CD36 activity which is measured is the ability to interact with **HSP** . The cell employed in (M1) comprises **HSP** that is non-covalently associated with an antigenic peptide, and the CD36 activity which is measured in the method is the ability to induce signal transduction activity, or to stimulate a cytotoxic T-cell response against the antigenic peptide. In (M2), CD36 present on a cell surface, or immobilized to a solid surface e.g. microtiter dish, is contacted with **HSP** . The amount of bound **HSP** is measured by contacting the cell with **HSP** -specific antibody. Optionally, the amount of **HSP** is labeled and the amount of bound **HSP** is measured by detecting the label, preferably a fluorescent label. In (M3), measuring level of stimulation of antigen-specific cytotoxic T-cells by CD36-expressing cells involves adding CD36-expressing cells formed in step (a) to T-cells under conditions conducive to the activation of the T-cells; and comparing the level of activation of cytotoxic T-cells with the level of activation of T-cells by CD36-expressing cell formed in the absence of the test compound, where an increase or decrease in level of T-cell activation indicates that a compound that modulates **HSP** -mediated signal transduction by CD36-expressing cells is identified. In all the above mentioned methods, the **HSP** is **gp96** . In (M4), the sample derived from a patient is contacted with an antibody specific for CD36 or **HSP** or **HSP** -CD36 complex, under conditions such that **immuno** specific binding by the antibody, takes place. In (M5), an agonist which enhances interaction of **HSP** and CD36 is employed. In (M6), an antagonist that interferes with the interaction between **HSP** and CD36 is employed. The antagonist is an antibody specific for **HSP** , a small molecule, or (P) as described above. Preferred Cell: (I) or (II) is a human cell. ACTIVITY - Antidiabetic; Neuroprotective; Nootropic; Antianemic; Antithyroid; Nephrotrophic; Virucide; Antibacterial; Antiparasitic; Cytostatic; **Immunosuppressive** ; Osteopathic; Antiinflammatory; Antilipemic. No supporting data is given. MECHANISM OF ACTION - **Immune** response modulator; **HSP** -CD36 interaction modulator. USE - (M1) is useful for identifying a compound (an agonist which enhances interaction of **HSP** with CD36, or antagonist which interferes with CD36) that modulates an **HSP** (preferably, **gp96**)-CD36-mediated process affecting autoimmune disorder, disease or disorder involving disruption or signal transducer activity, disease or disorder involving cytokine clearance or inflammation, proliferative disorder, **viral** disorder or other infectious disease, hypercholesterolemia, Alzheimer's disease, diabetes or osteoporosis. (M2) is useful for identifying the compound that modulates the binding of **HSP** (preferably **gp96**) to CD36. (M3) is useful for identifying the compound that modulates **HSP** (preferably **gp96**)-mediated signal transduction by CD36-expressing cells, where the signal transduction activity is production of nitric oxide or production of monocyte chemotactic protein (MCP)-1 chemokine. (M5) is useful for modulating an **immune** response. (M6) or (M7) is useful for treating an autoimmune disorder (all claimed). The autoimmune disease which are treated by the above mentioned methods are insulin dependent diabetes mellitus, multiple sclerosis, pernicious anemia, Graves's disease, Goodpasture's disease, etc. The compounds which modulate **HSP** -CD36 interaction are also useful treating infectious diseases caused by viruses, bacteria, parasites, and for treating proliferative cell disorders.

ADMINISTRATION - Administered by inhalation or insufflation (either through the mouth or the nose) or oral, buccal, parenteral or rectal administration. No specific clinical dosages are given. EXAMPLE - The identification of an interaction between **gp96** and the CD36 receptor present in macrophages and dendritic cells was carried out as follows. human embryo kidney (HEK) 923 cells were transfected using FuGENE 6 and a plasmid construct containing the CD36 cDNA. After a two day period to allow expression of the transgene, cells were harvested and incubated with varying concentrations of fluorescent protein probes (**GP96** - fluorescein isothiocyanate (FITC), Histone FITC, AcLDL-DiI, Ova-FITC and fatty acid free **bovine** serum albumin (BSA)-FITC. Cells were analyzed by flow cytometry. Low and high CD36 expressing populations were gated and analyzed for binding of proteins. The CD36 expressing cells bound to **GP96** -FITC where the non-expressing and CD36(low) did not bind. This binding was specific for **GP96** as demonstrated by the lack of any staining of the HEK293 cells of Histone-FITC, Ova-FITC, BSA (faf)-FITC. The positive control, acetylated low density lipoprotein, stained the CD36 expressing cells and did not stain the non-expressing CD36(low). Demonstrating that the transfected HEK93 cells express a functional CD36 protein and **gp96** binding is specific to CD36. To confirm that the transfected HEK 293 cells were properly expressing CD36, HEK293 transfected cells and mock transfected cells were incubated with a mouse anti-CD36 antibody and then stained with an anti-mouse-FITC antibody. The mock transfected cells did not stain, where the transfected cells were stained. When **gp96** -FITC was incubated with wild-type and CD36 null macrophages, a 52% loss of binding of **gp96** is exhibited by the CD36 null cells as compared to wild-type cells. When low density lipoprotein (LDL) or anti-CD36 was used as a competitive inhibitor for **gp96** binding, no inhibition occurred. This indicates that **gp96** does not bind to CD36 at a.a. 155-183 or a.a. 28-93, the respective binding regions of the anti-CD36 antibody and LDL, under the conditions test. Both wild type and CD36 null mice were injected with 0.2 ml pristane. Macrophages were extracted from such mice. Dendritic cells were extracted and cultured from bone marrow of non-pristane injected mice. Macrophages and dendritic cells were incubated for 20 hours in the presence of increasing concentrations of various native and denatured proteins (boiled for 30 minutes). The level of chemokine production from the mice was measured using standard enzyme linked **immunosorbant** assay (ELISA) sandwich assay. Native **gp96** induced a strong production of chemokine in both wild-type macrophages and dendritic cells as compared to the CD36 null population. Boiled **gp96** did not induce any chemokine production in either the wild-type macrophages and dendritic cells or the CD36 null macrophages and dendritic cells. Lipopolysaccharide (LPS) induced chemokine production but this was not due to CD36 because the level of chemokine production is greater in the CD36 null cells than in the wild-type cells. In addition, the level of chemokine was the same in both the native and boiled samples of LPS. Both the native and boiled HSP70 induced the same amount of chemokine in macrophages and dendritic cells in both the wild type and CD36 null cells demonstrating that this induction was not related to CD36. Tumor necrosis factor (TNF) and **bovine** serum albumin (BSA) induced an equal amount of chemokine production in both the wild-type and CD36 null cells also demonstrating that they do not act in chemokine production through CD36. Identical experiments were performed to determine the level of nitric oxide produced by wild-type and CD36 null cells. Macrophages and dendritic cells were incubated for 20 hours in the presence of increasing concentrations of various native and denatured proteins (boiled for 30 minutes) and the level of nitric oxide production was determined by the enzymatic Greisis assay. Native **gp96** induced a strong nitric oxide production in both macrophage and dendritic wild-type cells compared to the CD36 null cells. Boiled **gp96** did not

induce any nitric oxide production in either the wild-type macrophages and dendritic cells or the CD36 null macrophages and dendritic cells. LPS induced nitric cell production and this was not due to CD36 because the level of nitric oxide production is greater in the CD36 null cells than in the wild type cells. Both the native and boiled HSP70 induced the same amount of nitric oxide in macrophages and dendritic cells in both the wild-type and CD36 null cells demonstrating that this induction is not related to CD36. (93 pages)

Searched by M. Smith